

tetrahydrofuran, with an equimolecular amount of the corresponding organic or inorganic acid.

Examples of usable organic acids are the following: oxalic, tartaric, maleic, succinic, citric acid.

Examples of usable inorganic acids are the following: nitric, hydrochloric, sulphuric, phosphoric acid. Nitric and hydrochloric acid are preferred.

The compounds of the invention, as said, develop a marked protective action towards hepatopathies and in general towards diseases affecting the digestive apparatus, in particular the intestinal tract, in particular colites, gastrites, enterites, duodenites and hepatopathies. It has been found that the compounds of the invention in comparison with native precursors not only are not toxic as to the digestive apparatus, but unexpectedly they are able to prevent or reduce the diseases affecting this apparatus. For example the paracetamol efficacy as analgesic is known, however this compound causes damages at hepatic level (hepatic toxicity). The paracetamol nitrooxy derivatives according to the invention, besides being effective analgesic drugs, have no hepatic toxicity, but they are also able to prevent or reduce already existing hepatic damages.

The results obtained with the compounds of the invention are still more surprising if one considers that by using another NO donor such for example sodium nitroprussiate in pathologies affecting the digestive apparatus, there is no protection, on the contrary an hepatic damage occurs. Besides, this drug causes high hypotension.

As said, the compounds of the invention have a beneficial action also on tumoral processes, when used in the prophylaxis or in the therapy. As said, the pathologies on an inflammatory basis are considered precancerous forms, being able to subsequently evolve into tumoral processes. The pathologies on an inflammatory basis can involve various

systems such as the urogenital, respiratory, skin, digestive system, etc.

Therefore the treatment of these pathologies of inflammatory nature has a critical importance also in the prevention and in the treatment of tumoral diseases.

In the treatment of tumoral diseases the compounds of the invention can be used alone or in combination with known antitumoral treatments, such for example the administering of chemotherapeutic drugs, for example cis-platinum, adriamycin etc., or the radiotherapeutic treatment.

It has unexpectedly been found by the Applicant that the compounds of the invention, when used in combination with the above tumoral treatments, synergically enhance the therapeutic effect.

The administering of the compounds of the invention can be made contemporaneously with the chemotherapeutic or radiotherapeutic treatments, or previously or subsequently to the chemotherapeutic or radiotherapeutic treatments.

Preferably the compounds of the invention are used for the treatment and/or prevention of the tumoral process affecting the digestive apparatus. The preferred compounds are the above ones.

The compounds of the invention are prepared according to known methods of the prior art.

In general if in the drug molecule or in the molecules of the radicals Y and W more reactive groups such as for example COOH and/or HX are present, they must be protected before the reaction according to the known procedures of the prior art; for example as described in the volume by Th. W. Greene: "Protective groups in organic synthesis", Harward University Press, 1980.

Acyl halides are prepared according to known procedures of the prior art, for example by thionyl or oxalyl chloride,

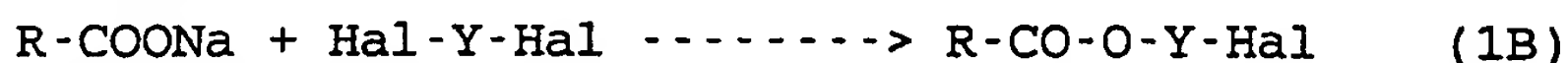
halides of P^{III} or P^V in solvents inert under the reaction conditions, such for example toluene, chloroform, DMF, etc.

1) When in formula (I) L is a covalent bond and $p = 0$, and the free valence of the drug radical R is saturated with a carboxylic group, the synthesis methods for obtaining the corresponding nitrooxyderivatives are the following:

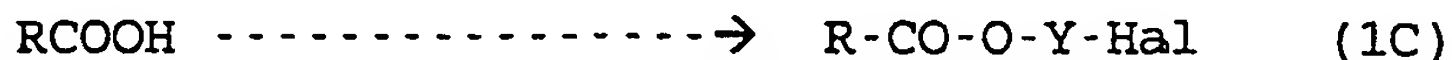
1.a) The acyl halide of the drug of formula $R-CO-Cl$ is reacted with an halogenalcohol of formula $HO-Y-Hal$, wherein Y is as above and Hal is halogen (Cl, Br, I).



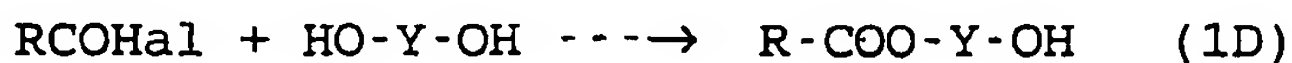
1.b) Alternatively, the reaction can be carried out by reacting the sodium or potassium salt of the drug with a dihalogen derivative of general formula $Y(Hal)_2$, wherein Y and Hal are as above defined.



1.c) Or the drug of formula $RCOOH$ is treated with an agent activating the carboxyl selected from N,N'-carbonyl diimidazol (CDI), N-hydroxybenzotriazole and dicyclohexylcarbodiimide in solvent such for example, DMF, THF, chloroform etc. at a temperature in the range $-5^\circ C$ - $50^\circ C$ and reacted in situ with a compound $HO-Y-Hal$, wherein Y and Hal are as above defined.

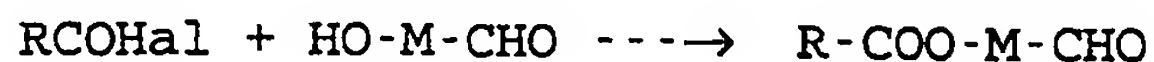


1.d) Alternatively, the acyl halide of the drug is reacted with a compound $HO-Y-OH$, wherein Y is as above, in the presence of a base, in an organic solvent inert under the reaction conditions according to the scheme reported hereunder:



1.e) Alternatively to the previous syntheses the acyl halide of the drug is reacted with a compound $HO-M-CHO$, wherein M is an aromatic ring having 6 carbon atoms, or a radical

Y^3 as above, in the presence of a base, in an organic solvent inert under the reaction conditions according to the scheme reported hereunder:



The obtained compound is subjected to hydrogenation in the presence of palladium on carbon to give the corresponding alcohol:



wherein Y is as above defined.

- 1.f) When the products obtained in the above reactions have formula $R-COO-Y-Hal$ the corresponding nitrooxyderivatives are obtained by reacting the compound $R-CO-O-Y-Hal$ with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran according to the scheme:



- 1.g) When the compounds obtained in the above reactions have formula $R-COO-Y-OH$ the corresponding nitrooxyderivatives can be obtained by treatment with fuming nitric acid in organic solvent under anhydrous conditions and in inert atmosphere, in the presence of an inorganic acid different from the nitric acid, or with an organic acid, or of an anhydride of one or two organic acids.

- 1.h) Alternatively, in the compound of formula $R-COO-Y-OH$ the hydroxyl group is subjected to halogenation, for example, with PBr_3 , PCl_5 , $SOCl_2$, $PPh_3 + I_2$, and then reacted with $AgNO_3$ in organic solvent such as acetonitrile, tetrahydrofuran.

- 2) When in formula (I) L is a covalent bond and $p = 0$, and the free valence of the radical R of the drug is saturated with a hydroxyl group, the synthesis methods for obtaining the corresponding nitrooxyderivatives are the following:

- 2.a) By reaction of the drug of formula R-OH with an acyl halide of formula Hal-Y-COHal, wherein Y and Hal are as above, according to the scheme:



- 2.b) By reaction of the drug of formula R-OH with an acyl halide of formula OH-Y-COHal, wherein Y and Hal are as above, according to the scheme:



- 2.c) When the compounds obtained in the above reactions have formula R-OCO-Y-Hal or R-OCO-Y-OH the corresponding nitrooxyderivatives are obtained as described in 1.f and 1.h respectively.

3. When in formula (I) $p = 1$ and $L = X$, wherein X is as above, or $L = \text{CO}$, and the free valence of the radical R of the drug is saturated with a carboxylic group, the synthesis methods for obtaining the corresponding nitrooxyderivatives are the following:

- 3.a) By reaction between the acyl halide of the drug and the compound of formula HX-Y-COOH, wherein X and Y are as above defined, according to the known methods of the prior art, to give the compound R-CO-X-Y-COOH which is transformed into the corresponding sodium salt and reacted with a compound of formula Hal-Y_T-R₈ wherein Hal and Y_T are as above and R₈ is Cl, Br, Iodine, OH:



If $R_8 = \text{OH}$ the compound of formula (3.A') is subjected to halogenation as described in 1.h); if $R_8 = \text{Hal}$ the compound of formula (3.A') is reacted with AgNO_3 in organic solvent such as acetonitrile, tetrahydrofuran:

- 3.b) When Y_T is a C₄ linear alkylene, the acid of formula (3.A) is reacted with triphenylphosphine in the presence of an halogenating agent such as CBr₄ or N-

bromosuccinimide in tetrahydrofuran to give the compound of formula (3.A') wherein $R_8 = \text{Br}$ which is transformed into the corresponding nitrooxyderivative as described in 1.h.

- 4) When in formula (I) $p = 1$ and $L = \text{X}$ or CO , and the free valence or the radical R of the drug is saturated with an hydroxyl group, the synthesis methods for obtaining the corresponding nitrooxyderivatives are the following:

- 4.a) Reaction of the drug of formula R-OH with an acyl halide of formula HX-Y-COHal , wherein X and Y are as above defined, according to the known methods of the prior art, to give the compound R-O-CO-Y-XH which is reacted with a compound of formula $\text{R}_8\text{-Y}_\text{T}\text{-COHal}$ wherein R_8 and Y_T are as above.



- 4.b) Alternatively, the drug of formula R-OH is reacted with a compound of formula HX-Y-COOH , wherein X and Y are as above, in the presence of dicyclohexylcarbodiimide as described in 1.c, to give the compound R-O-CO-Y-XH , which is reacted with a compound of formula $\text{R}_8\text{-Y}_\text{T}\text{-COCl}$ wherein R_8 and Y_T are as above defined to give the following compound: $\text{R-O-CO-Y-X-CO-Y}_\text{T}\text{-R}_8$ (4.B).

When $\text{R}_8 = \text{OH}$ the compound of formula (4.B) or of formula (4A') is subjected to halogenation as described in 1.h); if $\text{R}_8 = \text{Hal}$ the compound of formula (4.B) is reacted with AgNO_3 in organic solvent such as acetonitrile, tetrahydrofuran.

The compounds of the present invention are formulated in the corresponding pharmaceutical compositions for parenteral, oral and topical use according to the well known techniques in the field, together with the usual excipients; see for example the volume "Remington's Pharmaceutical Sciences 15a Ed."

The amount on a molar basis of the active principle in these formulations is the same, or lower, with respect to that used as antiinflammatory and/or analgesic drug of the corresponding precursor drug.

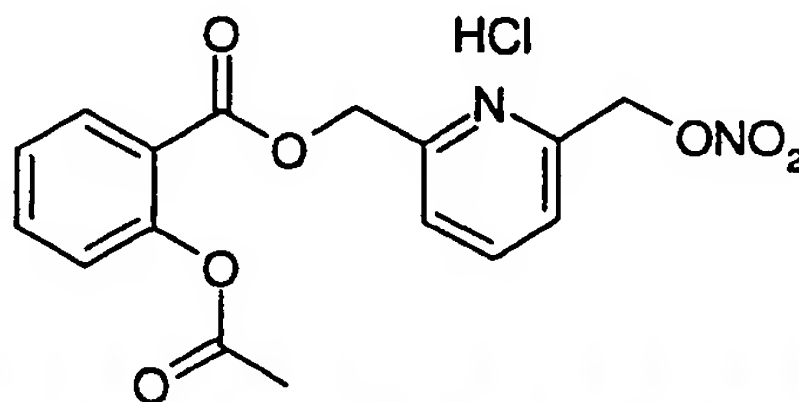
The daily administrable doses are those of the antiinflammatory and/or analgesic precursor drugs, or, in case, lower. The daily doses can be found in the literature of the field, such as for example in "Physician's Desk reference".

The following Examples illustrate the invention and they are not limitative of the scope of the same.

EXAMPLES

EXAMPLE 1

Synthesis of 2-acetyloxybenzoic acid 6-(nitrooxymethyl)-2-methylpyridinyl ester hydrochloride of formula:



A) Synthesis of 2,6-bis-(chloromethyl)pyridine

To thionyl chloride (11.6 ml, 158 mmol), cooled at 0°C, 2,6-bis-(hydroxymethyl)pyridine (4 g, 28 mmol) is added very slowly. The obtained solution is left under stirring for 2 hours at room temperature, then the thionyl chloride in excess is evaporated at a reduced pressure. The obtained residue is treated with chloroform and it is evaporated again at a reduced pressure to remove the thionyl chloride residues. The raw product is treated with chloroform and washed with water. The organic phase is anhydriified with sodium sulphate and dried obtaining 4,81 g of the product as white solid having melting point = 76-78°C.

B) Synthesis of 2-acetyloxybenzoic acid 6-(chloromethyl)-2-methylpyridinyl ester

To a solution of acetylsalicylic acid (1.6 g, 8.88 mmols) in N,N'-dimethylformamide (20 ml) and under stirring sodium ethylate (0.64 g, 8.88 mmols) is added. After 30 minutes the obtained solution is added to a solution of 2,6-bis-(chloromethyl)pyridine (4.72 g, 26.81 mmols) in N,N'-dimethylformamide (20 ml). The solution is left at room temperature for 7 days, under stirring, then it is diluted with ethyl ether and washed with water. The separated organic phases are anhydriified with sodium sulphate and the solvent is evaporated at a reduced pressure. The reaction raw product is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 1.7 g of the product as yellow oil are obtained.

¹H-NMR (200MHz)(CDCl₃): 8.10(1H,d); 7.74(1H,t); 7.57(1H,t); 7.42(1H,d); 7.33(2H,m); 7.11(1H,d); 5.42(2H,s); 4.67(2H,s); 2.41(3H,s).

C) Synthesis of 2-acetyloxybenzoic acid 6-(nitrooxymethyl)-2-methylpyridinyl ester

To a solution of 2-acetyloxybenzoic acid 6-(chloromethyl)-2-methylpyridinyl ester (1.5 g, 4.7 mmols) in acetonitrile (20 ml) kept under stirring, silver nitrate (1.3 g, 7.65 mmols) is added. The solution is heated up to 80°C, maintaining it sheltered from light, under stirring for 30 hours. The formed silver chloride is filtered, the solvent is evaporated. The reaction raw product is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 7/3. 1.2 g of product as yellow oil are obtained.

¹H-NMR (200MHz)(CDCl₃): 8.10(1H,d); 7.74(1H,t); 7.57(1H,t); 7.42(1H,d); 7.33(2H,m); 7.11(1H,d); 5.60(2H,s); 5.42(2H,s); 2.41(3H,s).

D) Synthesis of 2-acetyloxybenzoic acid 6-(nitrooxymethyl)-2-methylpyridinyl ester hydrochloride

To a solution of 2-acetyloxybenzoic acid 6-(nitrooxymethyl)-2-methylpyridinyl ester (1 g, 2.88 mmol) in ethyl acetate (20 ml) cooled at 0°C, a solution of ethyl acetate/HCl 5M is added dropwise under stirring. It is left for 1 hour at 0°C, then the temperature is let reach room values. The formed precipitate is filtered and washed with ethyl ether. 900 mg of solid product are obtained.

Elementary analysis

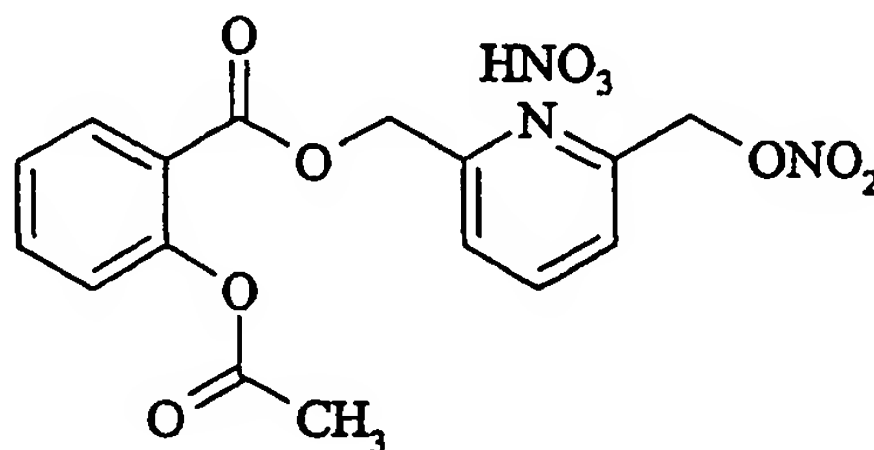
Calculated C 50.21% H 3.95% N 7.31% Cl 9.26%

Found C 50.23% H 3.97% N 7.29% Cl 9.20%

¹H NMR (200MHz) (CDCl₃): 8.10 (2H, m); 7.7 (1H, t); 7.56 (2H, d); 7.48 (1H, t); 7.30 (1H, d); 5.74 (2H, s); 5.43 (2H, s); 2.20 (3H, s).

EXAMPLE 2

Synthesis of 2-acetyloxybenzoic acid 6-(nitrooxymethyl)-2-methylpyridinyl ester nitrate of formula:



The 2-acetyloxybenzoic acid 6-(nitrooxymethyl)-2-methylpyridinyl ester nitrate is obtained starting from the 2-acetyloxybenzoic acid 6-(nitrooxymethyl)-2-methylpyridinyl ester isolated at step C) of Example 1.

To a solution of 2-acetyloxybenzoic acid-6-(nitrooxymethyl)-2-methylpyridinyl ester (1 g, 2.88 mmol) in acetonitrile (10 ml) cooled at 0°C, a solution of nitric acid 65% (0.2 ml) in acetonitrile (2 ml) is added dropwise under stirring. It is left for 2 hours at 0°C, then the temperature is let reach the room temperature. The formed precipitate is

filtered and washed with ethyl ether. One gram of product as a solid is obtained.

Elementary analysis

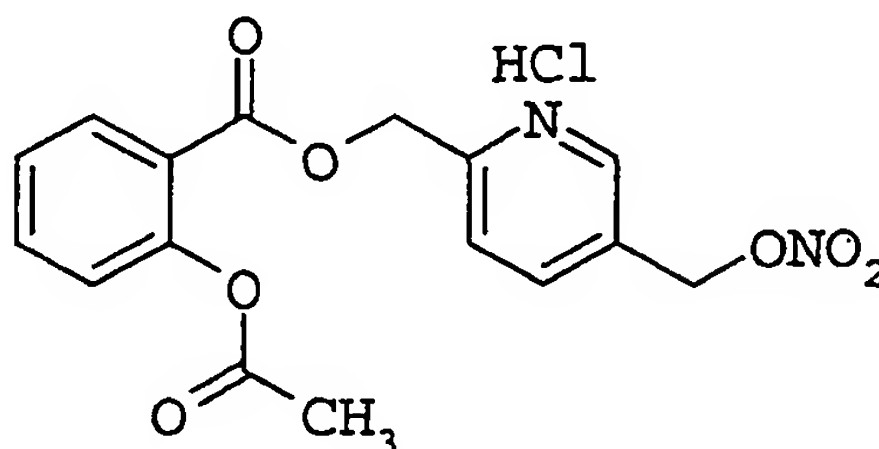
Calculated C 46.95% H 3.69% N 10.26%

Found C 46.99% H 3.72% N 10.22%

¹H NMR (200MHz) (CDCl₃): 8.10 (1H, d); 7.9 (1H, t); 7.79(1H, t); 7.5 (3H, m); 7.30(1H, d); 5.73 (2H, s); 5.42 (2H, s); 2.20 (3H, s).

EXAMPLE 3

Synthesis of 2-acetyloxybenzoic acid 5-(nitrooxymethyl)-2-methylpyridinyl ester hydrochloride of formula:



The 2-acetyloxybenzoic acid 5-(nitrooxymethyl)-2-methylpyridinyl ester hydrochloride is synthesized according to the process described in Example 1, starting from acetyl salicylic acid and 2,5-bis(chloromethyl)pyridine.

A) Synthesis of 2,5-bis(chloromethyl)-pyridine

The compound is synthesized according to the process described in Example 1 A) starting from 2,5-pyridin-dimethanol, synthesized in its turn by reduction with NaBH₄ of di-ethyl-2,5-pyridin dicarboxylate in ethanol as described in patent JP 48029783.

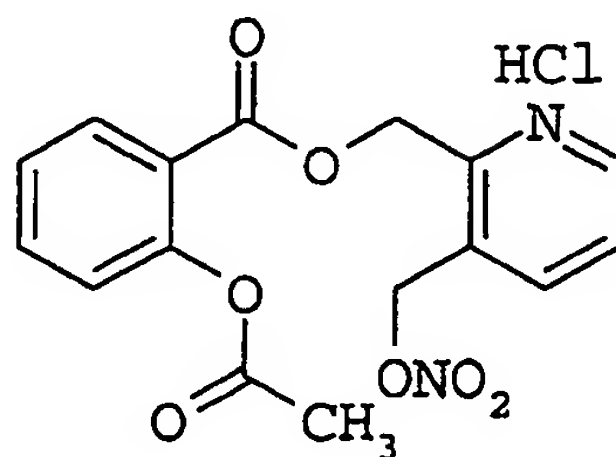
Elementary analysis

Calculated C 50.21% H 3.95% N 7.32% Cl 9.26%

Found C 50.19% H 3.92% N 7.37% Cl 9.28%

EXAMPLE 4

Synthesis of 2-acetyloxybenzoic acid 3-(nitrooxymethyl)-2-methylpyridinyl ester hydrochloride of formula:



The 2-acetyloxybenzoic acid 3-(nitrooxymethyl)-2-methylpyridinyl ester hydrochloride is synthesized according to the process described in Example 1, starting from acetyl salicylic acid and 2,3-bis(chloromethyl)pyridine.

A) Synthesis of 2,3-bis(chloromethyl)-pyridine

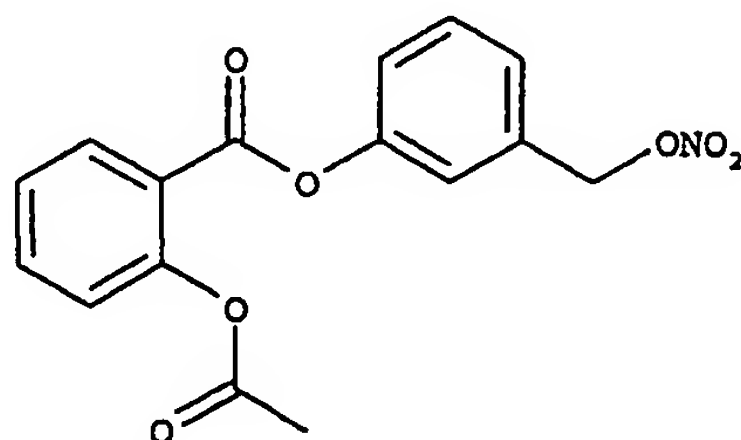
The compound is synthesized according to the process described in Example 1 A) starting from 2,3-pyridine dimethanol, synthesized in its turn by reduction with LiAlH_4 of di-methyl-2,3-pyridinedicarboxylate in ethanol as described in J. Chem. Soc., Perkin Trans. 1 (1972), (20), 2485-2490.

Elementary analysis

Calculated	C 50.21%	H 3.95%	N 7.32%	Cl 9.26%
Found	C 50.25%	H 3.93%	N 7.30%	Cl 9.29%

EXAMPLE 5

Synthesis of 3-nitrooxymethylphenyl ester of the 2-acetoxybenzoic acid



A) Preparation of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid

3-hydroxymethylphenol (10 g, 0.08 moles) is dissolved in toluene (50 ml) containing triethylamine (9.8 g, 0.1 moles).

To the so obtained solution, a solution of the acetylsalicylic acid chloride (16 g, 0.08 moles) in toluene (50 ml) is added under stirring at the temperature of 5-10°C. The mixture is maintained at a temperature within the above range, under stirring for 2 hours, then poured into water and then extracted with dichloromethane (2 x 100 ml). The organic phase is separated, washed in sequence with a solution of potassium carbonate at 25% w/v, with water, with a 3% hydrochloric acid solution and finally again with water, then anhydriified with sodium sulphate and the solvent evaporated under reduced pressure. The residue is crystallized from isopropanol.. 3-hydroxymethyl phenyl ester of the 2-acetoxybenzoic acid (45.8 g, 0.16 moles, yield 80%) is obtained.

M.p.: 79-81°C.

^1H NMR(CDCl₃) δ (ppm): 2.29 (s, 3H); 4.71 (s, 2H); 7.07-8,2 (m, aromatics, 8H).

B) Nitration with fuming nitric acid, in the presence of sulphuric acid, of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid

A solution of fuming nitric acid (3.92 g, 62.2 mmoles, 3 moles with respect to the moles of the hydroxyester under reaction) and sulphuric acid 96% (6.10 g, 62.2 mmoles, 3 moles with respect to the moles of the hydroxyester under reaction) in dichloromethane (25 ml) is cooled to 0°C and added in one hour time under stirring and under nitrogen atmosphere, with a solution of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (6 g, 20.7 mmoles) in 25 ml of dichloromethane. The mixture is then diluted with dichloromethane (50 ml) and

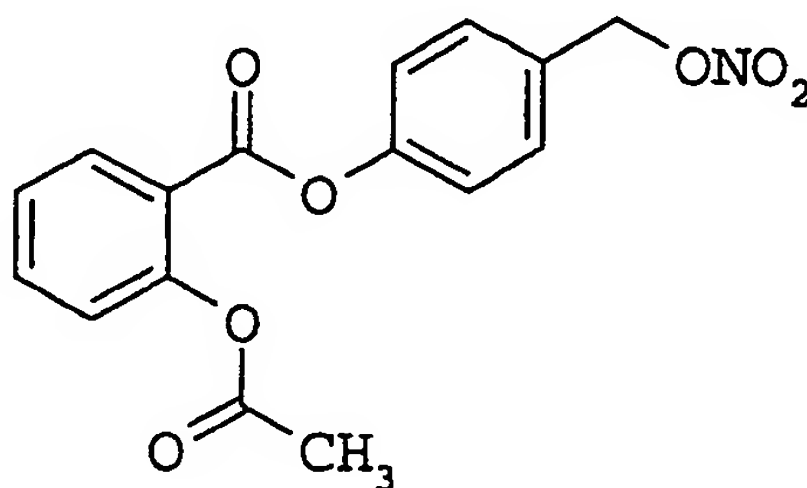
poured into water and ice (100 g). The organic phase is separated, washed with water, anhydried with sodium sulphate and the solvent evaporated under reduced pressure. The residue is crystallized from isopropanol obtaining the 3-nitrooxymethylphenyl ester of the 2-acetoxybenzoic acid (5.6 g, 17 mmols, yield 82%).

M.p.: 61-62°C.

^1H NMR(CDCl_3) δ (ppm): 2.31 (s, 3H); 5.44 (s, 2H); 7.16-8.22 (m, aromatics, 8H).

EXAMPLE 6

Synthesis of 2-(acetyloxy)benzoic acid 4-(nitrooxymethyl)phenyl ester



A) Synthesis of 2-(acetoxy)benzoic acid 3-(formyl)phenyl ester

To a mixture of 4-hydroxybenzaldehyde (20.75 g, 0.17 moles) and triethylamine (0.205 g, 2.4 mmols) in methylene chloride (300 ml) kept under stirring, under nitrogen inert atmosphere, cooling at a temperature in the range -5°C-0°C, acetylsalicyloil chloride (41.25 g, 0.21 moles) is added in small aliquots in one hour. After 15 minutes water (250 ml) is added and the phases are separated. The aqueous phase is recovered and separately extracted with methylene chloride. The organic phases are mixed together, they are washed with a 5% carbonate solution (150 ml x 2) and then with water (125 ml x 2). The organic phase is anhydried with sodium sulphate in the presence of decolorating carbon. It is filtered under vacuum and the solvent is evaporated under reduced pressure and at a bath temperature lower than 40°C, obtaining 48.2 g of

2-(acetyloxy)benzoic acid 4-(formyl)phenyl ester. The reaction raw product is used without further purification.

B) Synthesis of 2-(acetyloxy)benzoic acid 4-(hydroxymethyl)phenyl ester

A solution of 2-(acetyloxy)benzoic acid 4-(formyl)phenyl (48.2 g, 0.18 moles) ester in ethyl acetate (500 ml) is hydrogenated in the presence of 5% palladium on carbon (4 g) at room temperature, at hydrogen pressure of about 2.5 atm, under stirring. After 30 minutes the reactor is discharged, the catalyst is removed by filtration under nitrogen atmosphere.

The organic phase is washed with a 5% sodium bicarbonate solution and then with water. It is anhydriified with sodium sulphate and the solvent is evaporated at reduced pressure and the residue is used without further purification.

C) Synthesis of 2-(acetyloxy)benzoic acid 4-(chloromethyl)phenyl ester

To a mixture of 2-(acetyloxy)benzoic acid 4-(hydroxymethyl)phenyl (51.5 g, 0.18 moles) and SOCl_2 (153 ml) kept under stirring, dimethylformamide (140 ml) is added at room temperature and it is left under stirring for one hour. At the end the thionyl chloride is evaporated at reduced pressure at a bath temperature lower than 40°C. The thionyl chloride traces in the compound are removed by treating the solid with toluene (60 x 2), which is then removed by evaporation at reduced pressure at a bath temperature lower than 40°C. The raw product is purified by crystallization with isopropyl ether to give 2-(acetyloxy)benzoic acid 4-(chloromethyl)phenyl ester (32.9 g, 0.10 moles). Yield 60%.

^1H NMR: 8.25 (1H, d); 7.68 (1H, t); 7.43 (3H, m); 7.20 (3H, m); 4.60 (2H, s); 2.34 (3H, s).

D) Synthesis of 2-(acetyloxy)benzoic acid 4-(nitrooxymethyl)phenyl ester

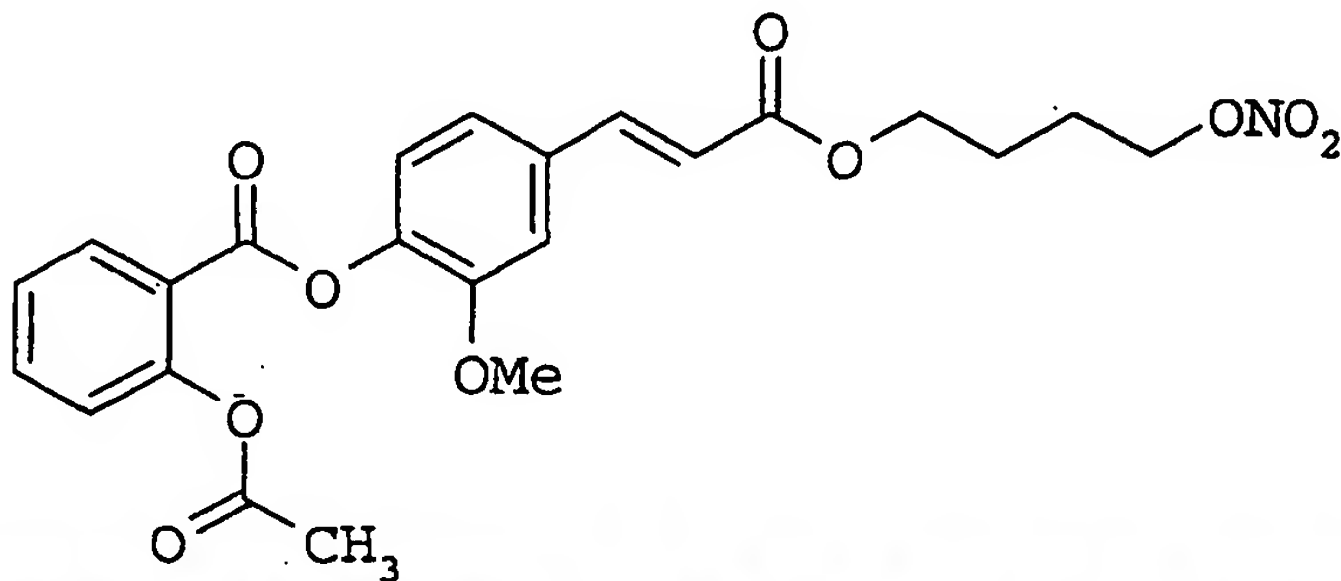
To a solution of 2-(acetyloxy)benzoic acid 4-(chloromethyl)phenyl ester (32.9 g, 0.10 moles) in acetonitrile silver nitrate (22.2 g, 0.12 moles) is added under stirring, sheltered from light. The solution is heated at 70°C for 4 hours and then cooled to room temperature. The precipitate is filtered and the solvent evaporated at reduced pressure.

The residue is purified by chromatography on silica gel eluting with hexane/ethyl acetate (7:3 v/v) to give 2-(acetyloxy)benzoic acid 4-(nitrooxymethyl)phenyl ester (16.6 g, 0.05 moles). M.p. 86-88°C. Yield 50%.

¹H NMR (CDCl₃): 8.21 (1H, dd); 7.66 (1H, dt); 7.42 (3H, m); 7.20 (3H, m); 5.40 (2H, s), 2.25 (3H, s).

EXAMPLE 7

Synthesis of trans -3-[4-[2-(acetyloxy)benzoyloxy]-3-methoxyphenyl]-2-propenoic acid 4-(nitrooxy) butyl ester



A) Synthesis of trans -3-[4-hydroxy-3-methoxyphenyl]-2-propenoic acid 4-bromo butyl ester

To a solution of ferulic acid (10 g, 51.5 mmols) in THF (400 ml) and cooled in a water bath, triphenylphosphine (27.01 g, 103 mmols) and carbon tetrabromide (34.1 g, 103 mmols) are in the order added. The mixture is kept under stirring for 5 hours at room temperature. When the reaction is ended, triphenylphosphin oxide is filtered and the solvent is evaporated at reduced pressure. The residue is purified by

chromatography on silica gel eluting with hexane/ethyl acetate (7:3 v/v). 7.75 g of trans -3-[4-hydroxy-3-methoxyphenyl]-2-propenoic acid 4-bromobutyl ester as a white solid are obtained. M.p. 86-89°C. Yield 46%.

B) Synthesis of trans -3-[4-[2-(acetyloxy) benzoyloxy]-3-methoxyphenyl]-2-propenoic acid 4-bromo butyl ester

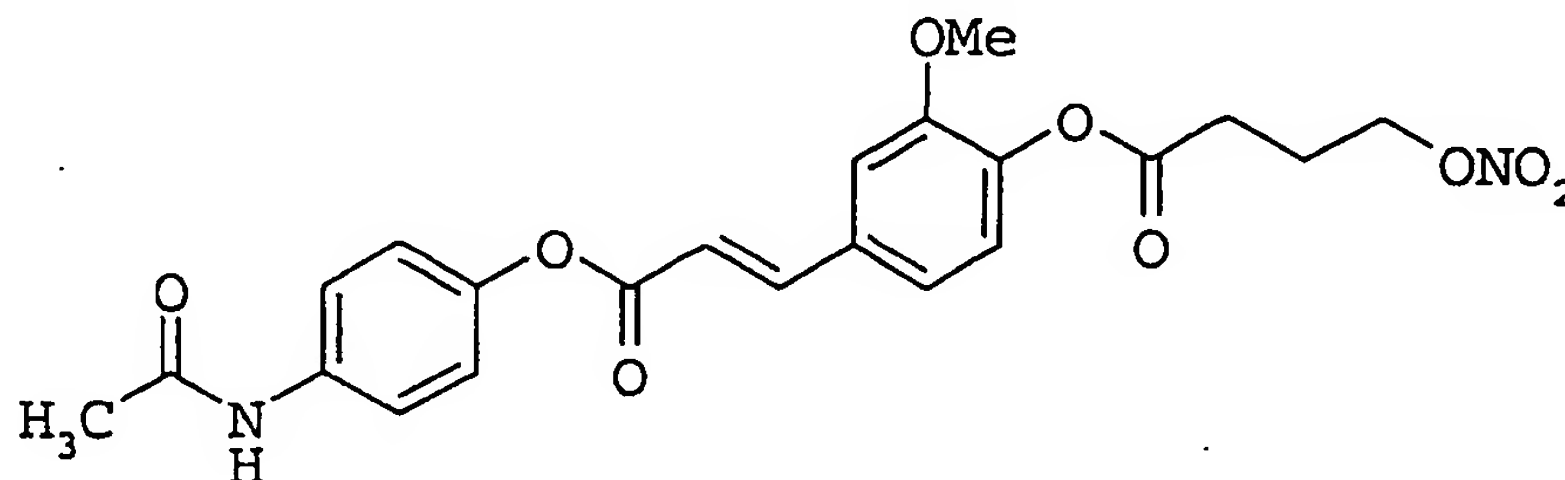
To a solution of trans 3-[4-hydroxy-3-methoxyphenyl]-2-propenoic acid 4-bromo butyl ester (2 g, 6.1 mmol) in CHCl_3 (20 ml) an acetylsalicylic acid mixture (1.1 g, 6.1 mmol) in DMF (2 ml) is added and it is cooled to 0°C, then DCC (1.50 g, 7.2 mmol) and DMAP (74 mg, 6×10^{-3} mmol) are added. It is left at the same temperature for 30 minutes and at room temperature for 16 hours. The precipitate is filtered and the solvent is evaporated at reduced pressure. The residue is dissolved in ethyl acetate (100 ml x 2 times) and washed with water and NaCl. The organic phase is anhydriified and the solvent is evaporated at reduce pressure.

The residue is purified by chromatography on silica gel eluting with hexane/ethyl acetate (8:2 v/v) to give the trans -3-[4-[2-(acetyloxy)benzoyloxy]-3-methoxyphenyl]-2-propenoic acid 4-bromo butyl ester (1.1 g, Yield 37%).

^1H NMR CDCl_3 : 8.25 (1H, d); 7.65 (2H, m); 7.40 (1H, t); 7.20 (4H, m); 6.39 (1H, d); 4.25 (2H, t); 3.85 (3H, s); 3.47 (2H, t); 2.29 (3H, s); 2.01 (2H, m); 1.89 (2H, m).

EXAMPLE 8

Synthesis of trans-3-[4-(4'-nitrooxybutyryloxy)-3-methoxyphenyl]-2-propenoic acid 4-(acetylamino)phenyl ester



A) Synthesis of trans-3-[4-acetyloxy-3-methoxyphenyl]-2-propenoic acid

To a solution of ferulic acid (5 g, 25.75 mmol) in pyridine (75 ml) cooled to 0°C and sheltered from light, acetic anhydride (13.14 g, 128.7 mmol) is added in small aliquots. When the addition is ended the temperature is let reach the room value maintaining the solution under magnetic stirring for 24 hours. HCl 18.5 % (160 ml) is added up to pH 2, one extracts with ethyl acetate and the organic phase is anhydried and the solvent is evaporated at a reduced pressure. 5.15 g of trans-3-[4-acetyloxy-3-methoxyphenyl]-2-propenoic acid are obtained as a white solid. M.p. 199-205°C. Yield 85%.

B) Synthesis of trans-3-[4-acetyloxy-3-methoxyphenyl]-2-propenoyl chloride

To a suspension of trans-3-[4-acetyloxy-3-methoxyphenyl]-2-propenoic acid (4 g, 16.93 mmol) in toluene (70 ml) and dimethylformamide (10 ml) cooled in an ice bath, oxalyl chloride (4.30 g, 33.87 mmol) is dropped. The mixture is maintained under stirring at 0°C for 1 hour then the temperature is let reach the room value and it is left for 2 hours. The solvent is removed at reduced pressure and the raw product is used without further purification.

C) Synthesis of trans-3-[4-acetyloxy-3-methoxyphenyl]-2-propenoic acid 4-(acetylamino)phenyl ester

To a solution of paracetamol (2.56 g, 16.92 mmol) in pyridine (20 ml) cooled in an ice bath trans-3-[4-acetyloxy-3-methoxyphenyl]-2-propenoyl chloride (4.31 g, 16.92 mmol) dissolved in acetone (45 ml) is dropped. The mixture is maintained under stirring in ice for 3 hours then it is poured into water (300 ml) and the precipitate is filtered and triturated with hexane to give trans-3-[4-acetyloxy-3-methoxyphenyl]-2-propenoic acid 4-(acetylamino)phenyl ester (4.38 g) as an orange solid. M.p. 246-250°C. Yield 70%.

D) Synthesis of trans-3-[4-hydroxy-3-methoxyphenyl]-2-propenoic acid 4-(acetylamino)phenyl ester

To a solution of trans-3-[4-acetyloxy-3-methoxyphenyl]-2-propenoic acid 4-(acetylamino)phenyl ester (4.2 g, 11.37 mmols) in methanol (650 ml) and tetrahydrofuran (850 ml), potassium carbonate (9.11 g, 65.95 mmols) dissolved in water (50 ml) is added and it is left under stirring at room temperature for 2 hours. The precipitate is filtered and the solution is brought to pH 6 with HCl 5% (15 ml). One extracts with ethyl acetate and the organic phase is anhydriified and removed from the solvent at reduced pressure. The raw product is purified by chromatography on silica gel eluting with chloroform/methanol (9/0.5 v/v). Trans-3-[4-hydroxy-3-methoxyphenyl]-2-propenoic acid 4-(acetylamino)phenyl ester (2.1 g) is obtained as a white solid. M.p. 185-195°C. Yield 56%.

¹H NMR (CDCl₃): 10 (1H, s); 9.8 (1H, s); 7.8 (1H, d); 7.7 (2H, d); 7.3 (2H, d); 7.1 (2H, d); 6.9 (1H, d); 6.7 (1H, d); 3.8 (3H, s); 2 (3H, s).

E) Synthesis of trans-3-[4-(4'-bromobutyryloxy)-3-methoxyphenyl]-2-propenoic acid 4-(acetylamino)phenyl ester

To a solution of trans-3-[4-hydroxy-3-methoxyphenyl]-2-propenoic acid 4-(acetylamino)phenyl ester (1.6 g, 4.8 mmols) in pyridine (12 ml) cooled in ice bath, 4-bromobutyryl chloride (1.3 g, 7.2 mmols) dissolved in acetone (15 ml) is dropped and it is maintained under stirring for 7 hours. It is poured into water and ice, the precipitate is filtered and treated with hexane. Trans-3-[4-(4'-bromobutyryloxy)-3-methoxyphenyl]-2-propenoic acid 4-(acetylamino)phenyl ester (1.8 g) is obtained. Yield 67%.

F) Synthesis of trans-3-[4-(4'-nitrooxybutyryloxy)-3-methoxyphenyl]-2-propenoic acid 4-(acetylamino)phenyl ester

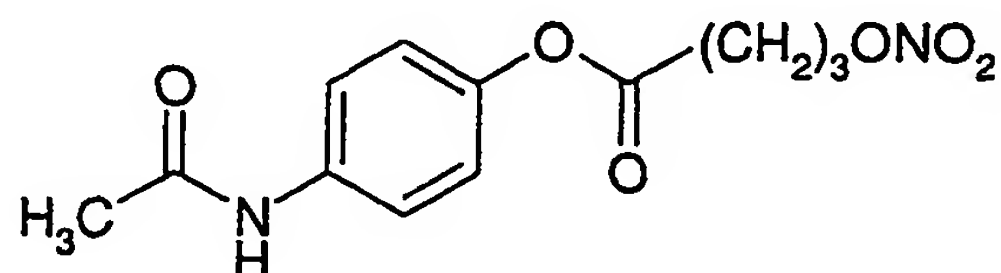
To a solution of trans-3-[4-(4'-bromobutyryloxy)-3-methoxyphenyl]-2-propenoic acid 4-(acetylamino)phenyl ester

(1.8 g, 3.78 mmol) in acetonitrile (100 ml), silver nitrate (1.28 g, 7.56 mmol) is added sheltered from light. It is left at 80°C for 13 hours then the precipitate is filtered. The raw product is purified by chromatography on silica gel eluting with hexane/ethyl acetate (3/7 v/v). Trans-3-[4-(4'-nitrooxy-butyryloxy)-3-methoxyphenyl]-2-propenoic acid 4-(acetylamino)phenyl ester is obtained.

¹H NMR (CDCl₃): 7.8 (1H, d); 7.5 (3H, m); 7.1 (5H, m); 6.5 (1H, d); 4.6 (2H, t); 3.8 (3H, s); 2.7 (2H, t); 2.17 (5H, m).

EXAMPLE 9

Synthesis of 4-nitrooxybutanoic acid 4'-acetylamino phenyl ester



A) Preparation of 4-bromobutanoic acid 4'-acetylamino phenyl ester

To a solution of 4-bromobutyric acid (4.6 g, 27.6 mmol) in chloroform (45 ml) and N,N-dimethylformamide (20 ml), paracetamol (4.17 g, 27.6 mmol), N,N'-dicyclohexyl carbodiimide (8.42 g, 40.8 mmol) and 4-dimethylaminopyridine (0.15 g, 1.25 mmol) are added. The reaction mixture is kept under stirring at room temperature for 72 hours, filtered and evaporated under vacuum. The reaction raw product is treated with ethyl acetate and washed with brine and then with water. The organic phase is anhydriified with sodium sulphate and then evaporated under vacuum.

The residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 4/6 (v/v ratio). 5.33 g of the product as a white solid ar obtained.

M.p.= 108-110°C.

B) Preparation of 4-nitrooxybutanoic acid 4'-acetylamino phenyl ester

To a solution of 4-bromobutanoic acid 4'-acetylamino phenyl ester (5.33 g, 17.8 mmol) in acetonitrile (80 ml) silver nitrate (4.56 g, 26.9 mmol) is added. The reaction mixture is heated for 16 hours in absence of light at 80°C, then cooled to room temperature, filtered for removing the silver salts, and evaporated at reduced pressure. The residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 4/6. 4.1 g of the product as a white solid are obtained.

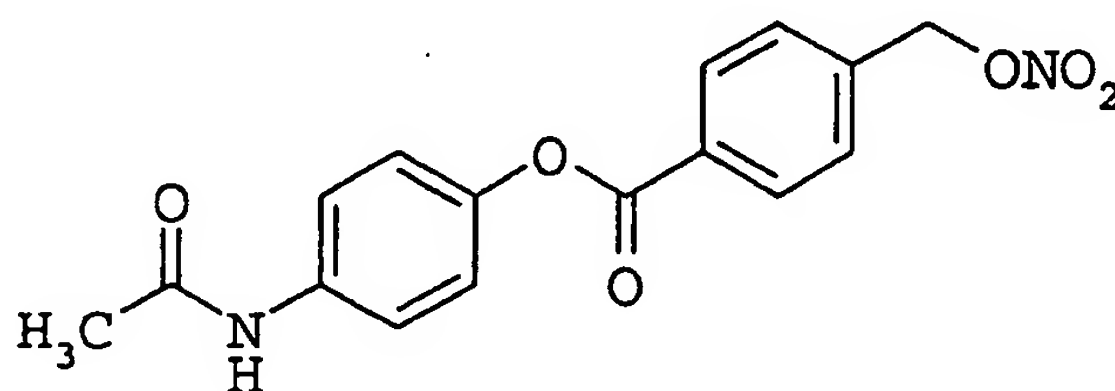
M.p. = 80-83°C.

Elementary analysis:	C	H	N
calc.	51.07%	4.99%	9.92%
found	51.06%	5.00%	9.90%

¹H NMR (CDCl₃): 7.55 (1H, s); 7.49 (2H, d); 7.02 (2H, d); 4.58 (2H, t); 2.71 (2H, t); 2.19 (2H, m); 2.14 (3H, s).

EXAMPLE 10

Synthesis of 4-(nitrooxymethyl)-benzoic acid 4'-acetylamino phenyl ester



A) Preparation of 4-(chloromethyl)-benzoic acid 4'-acetylamino phenyl ester

To a solution of paracetamol (2 g, 13.23 mmol) in tetrahydrofuran (80 ml), triethylamine (1.34 g, 13.23 mmol) and 4-(chloromethyl)-benzoylchloride (2.5 g, 13.23 mmol) are added. The reaction mixture is kept under stirring at room temperature for 24 hours, then the solvent is evaporated at reduced pressure and the reaction raw product is purified by chromatography on silica gel, eluting with methylene

chloride/methanol 20/0.5 (v/v ratio) to give 2.6 g of 4-(chloromethyl)-benzoic acid 4-acetylamino phenyl ester. (Yield 65%)

^1H NMR (CDCl_3): 8.1 (2H, d); 7.69 (2H, d); 7.45 (2H, d); 7.02 (2H, d); 4.9 (2H, s); 2.14 (3H, s).

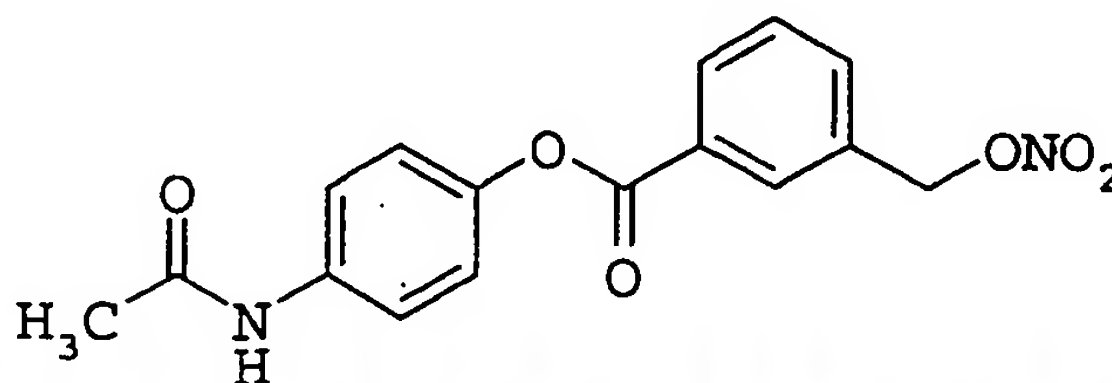
B) Preparation of 4-(nitrooxymethyl)-benzoic acid 4-acetylamino phenyl ester

To a solution of 4-(chloromethyl)-benzoic acid 4-acetylamino phenyl ester (2 g, 6.6 mmol) in acetonitrile (80 ml) silver nitrate (2.24 g, 13.18 mmol) is added. The reaction mixture is heated for 20 hours in absence of light at 60°C, then cooled to room temperature, filtered for removing the silver salts, and evaporated at reduced pressure. The residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 3/7 (v/v ratio). 1.13 g of 4-(nitrooxymethyl)-benzoic acid 4-acetylamino phenyl ester are obtained. (Yield 52%)

^1H NMR (CDCl_3): 8.1 (2H, d); 7.69 (2H, d); 7.45 (2H, d); 7.02 (2H, d); 5.74 (2H, s); 2.14 (3H, s).

EXAMPLE 11

Preparation of 3-(nitrooxymethyl)-benzoic acid 4-acetylamino phenyl ester



A) Preparation of 3-(chloromethyl)-benzoic acid 4-acetylamino phenyl ester

To a solution of paracetamol (2 g, 13.23 mmol) in tetrahydrofuran (80 ml), triethylamine (1.34 g, 13.23 mmol) and 4-(chloromethyl)-benzoylchloride (2.5 g, 13.23 mmol) are added. The reaction mixture is kept under stirring at room temperature for 24 hours, then the solvent is evaporated at

reduced pressure and the reaction raw product is purified by chromatography on silica gel, eluting with methylene chloride/methanol 20/0.5 (v/v ratio) to give 2.9 g of 3-(chloromethyl)-benzoic acid 4-acetylamino phenyl ester. (Yield 73%)

^1H NMR (CDCl_3): 8.1 (1H, s); 8.02 (1H, d); 7.77 (1H, d); 7.65 (1H, m); 7.45 (2H, d); 7.02 (2H, d); 4.9 (2H, s); 2.14 (3H, s).

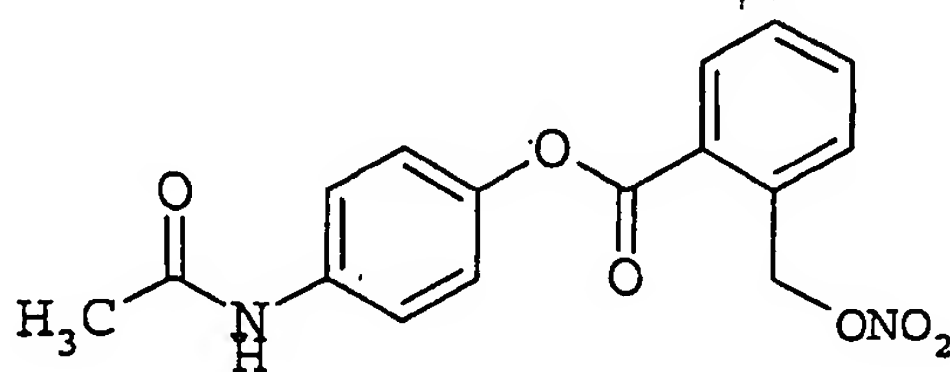
B) Preparation of 3-(nitrooxymethyl)-benzoic acid 4-acetylamino phenyl ester

To a solution of 3-(chloromethyl)-benzoic acid 4-acetylamino phenyl ester (2.5 g, 8.2 mmol) in acetonitrile (80 ml) silver nitrate (2.8 g, 16.4 mmol) is added. The reaction mixture is heated for 20 hours in absence of light at 60°C, then cooled to room temperature, filtered for removing the silver salts, and evaporated at reduced pressure. The residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 3/7 (v/v ratio). 1.5 g of 3-(nitrooxymethyl)-benzoic acid 4-acetylamino phenyl ester are obtained. (Yield 55%)

^1H NMR (CDCl_3): 8.1 (1H, s); 8.02 (1H, d); 7.77 (1H, d); 7.65 (1H, m); 7.45 (2H, d); 7.02 (2H, d); 5.74 (2H, s); 2.14 (3H, s).

EXAMPLE 12

Synthesis of 2-(nitrooxymethyl)-benzoic acid 4-acetylamino phenyl ester



A) Preparation of 2-(chloromethyl)-benzoylchloride

To thionyl chloride (35 ml) cooled at 0°C with ice bath, the 2-hydroxymethylbenzoic acid (4 g, 26.3 mmol) is added. The temperature is let reach the room value and the mixture is left under stirring for 2 hours, then it is evaporated at

reduced pressure and treated 3 times with chloroform for completely removing the thionyl chloride. The reaction raw product is used without further purification.

B) Preparation of 2-(chloromethyl)-benzoic acid 4-acetyl amino phenyl ester

To a solution of paracetamol (2 g, 13.23 mmol) in tetrahydrofuran (80 ml), triethylamine (1.34 g, 13.23 mmol) and 2-(chloromethyl)-benzoylchloride (2.5 g, 13.23 mmol) are added. The reaction mixture is kept under stirring at room temperature for 24 hours, then the solvent is evaporated at reduced pressure and the reaction raw product is purified by chromatography on silica gel, eluting with methylene chloride/methanol 20/0.5 (v/v ratio) to give 1.9 g of 2-(chloromethyl)-benzoic acid 4-acetyl amino phenyl ester. (Yield 47%)

¹H NMR (CDCl₃): 8.22 (1H, d); 7.41 (5H, m); 7.02 (2H, d); 4.9 (2H, s); 2.14 (3H, s).

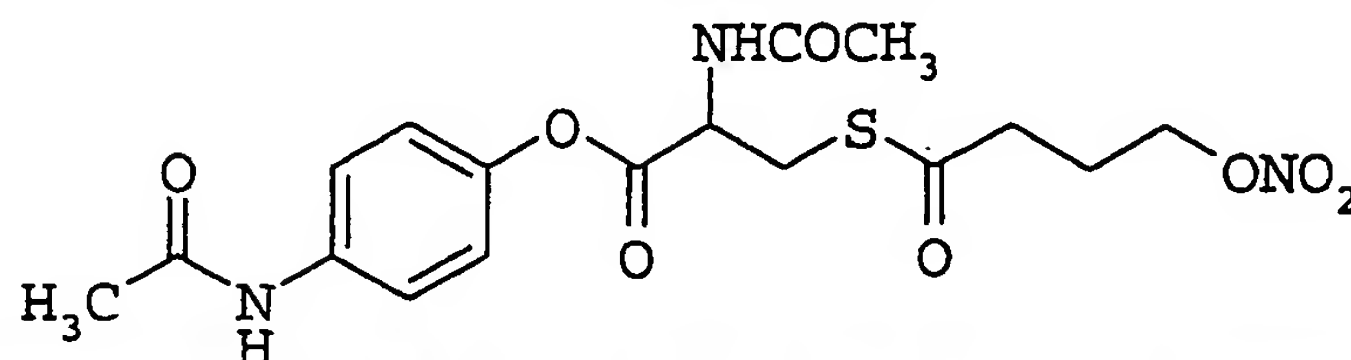
C) Preparation of 2-(nitrooxymethyl)-benzoic acid 4-acetyl amino phenyl ester

To a solution of 2-(chloromethyl)-benzoic acid 4-acetyl amino phenyl ester (1.5 g, 4.9 mmol) in acetonitrile (80 ml) silver nitrate (1.68 g, 9.8 mmol) is added. The reaction mixture is heated for 20 hours in absence of light at 60°C, then cooled to room temperature, filtered for removing the silver salts, and evaporated at reduced pressure. The residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 3/7 (v/v ratio). 0.77 g of 2-(nitrooxymethyl)-benzoic acid 4-acetyl amino phenyl ester are obtained. (Yield 48%)

¹H NMR (CDCl₃): 8.22 (1H, d); 7.41 (5H, m); 7.02 (2H, d); 5.40 (2H, s); 2.14 (3H, s).

EXAMPLE 13

Synthesis of 2-acetylamino-3-(4-nitrooxybutyryl)-3-mercapto-propionic acid 4-acetylamino phenyl ester



A) Preparation of 2-acetylamino-3-(4-bromobutyryl)-3-mercaptopropionic acid

To a solution of 4-bromobutyric acid (3 g, 17.9 mmol) in 35 ml of chloroform, carbonyl-diimidazol (2.9 g, 17.9 mmol) is added and it is left under stirring at room temperature for one hour. Then N-acetylcysteine (2.9 g, 17.9 mmol), sodium ethylate (40 mg, 0.58 mmol) and dimethylformamide (5 ml) are added and the mixture is left under stirring at room temperature for 15 hours. Diluted HCl is added and the organic phase is separated. The aqueous phase brought to pH 3-3.5 is extracted with ethyl acetate. The organic phases mixed together are anhydriified with sodium sulphate and evaporated at reduced pressure. The reaction raw product is purified by chromatography on silica gel, eluting with chloroform/ethyl acetate 3/7 (v/v ratio). 2.06 g of 2-acetylamino-3-(4-bromobutyryl)-3-mercapto-propionic acid are obtained. (Yield 37%)

¹H NMR (CDCl₃): 10.0 (1H, s); 6.89 (1H, d); 4.78 (1H, m); 3.40 (4H, m); 2.77 (2H, t); 2.18 (2H, m); 2.04 (3H, s).

B) Preparation of 2-acetylamino-3-(4-bromobutyryl)-3-mercaptopropionic acid 4-acetylamino phenyl ester

To a solution of 2-acetylamino-3-(4-bromobutyryl)-3-mercaptopropionic acid in chloroform (20 ml) and dimethylformamide (20 ml), cooled at 0°C with ice bath, paracetamol (1 g, 7.2 mmol), dicyclohexylcarbodiimide (1.17 g, 5.6 mmol) and N,N-dimethyl aminopyridine (90 mg) are added. The

temperature is let reach the room value and the mixture is left under stirring for 24 hours. The precipitate is filtered and the organic phase is washed with water. The organic phase is anhydrified with sodium sulphate and the solvent is evaporated at reduced pressure. The raw product has been purified by chromatography on silica gel eluting with methylene chloride/methanol 20/0.5 (v/v ratio). 0.6 g of 2-acetylamino-3-(4-bromobutyryl)-3-mercaptopropionic acid 4-acetylamino phenyl ester are obtained. (Yield 32%)

^1H NMR (CDCl_3): 7.45 (2H, d); 7.00 (2H, m); 4.80 (1H, m); 3.52 (2H, t); 3.32 (2H, d); 2.7 (2H, t); 2.1 (2H, m); 2.00 (3H, s).

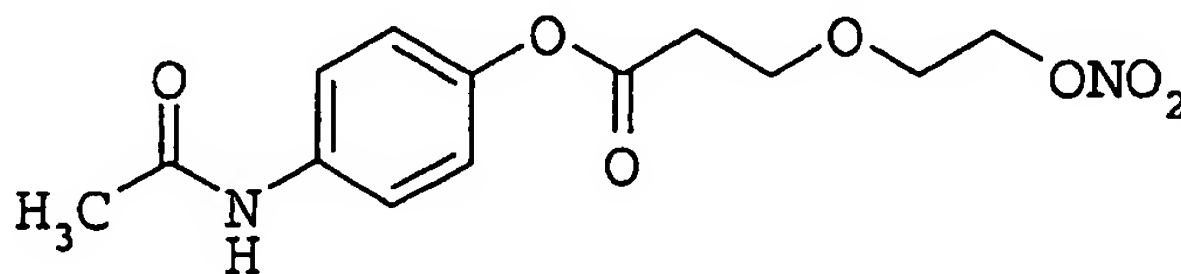
C) Preparation of 2-acetylamino-3-(4-nitrooxy butyryl)-3-mercaptopropionic acid 4-acetylamino phenyl ester

To a solution of 2-acetylamino-(4-bromobutyryl)-3-mercaptopropionic acid 4-acetylamino phenyl ester (0.5 g, 1.26 mmoles) in acetonitrile (40 ml) silver nitrate (0.43 g, 2.52 mmoles) is added. The reaction mixture is heated for 20 hours in absence of light at 80°C, then cooled to room temperature, filtered for removing the silver salts, and evaporated at reduced pressure. The residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 3/7 (v/v ratio). 0.31 g of 2-acetylamino-3-(4-nitrooxybutyryl)-3-mercaptopropionic acid 4-acetylamino phenyl ester are obtained. (Yield 63%)

^1H NMR (CDCl_3): 7.45 (2H, d); 7.00 (2H, m); 4.80 (1H, m); 4.57 (2H, t); 3.32 (2H, d); 2.7 (2H, t); 2.1 (2H, m); 2.00 (3H, s).

EXAMPLE 14

Synthesis of 3-[(2-nitrooxy)ethyloxy]propanoic acid 4-acetylamino phenyl ester



A) Preparation of 3-[(2-hydroxy)ethyloxy]propanoic acid 4-acetylamino phenyl ester

To a solution of paracetamol (5 g, 33.6 mmol) in chloroform (80 ml) and dimethylformamide (80 ml), cooled at 0°C with ice bath, 3-[(2-hydroxy)ethyloxy]propanoic acid (3 g, 22.38 mmol), dicyclohexylcarbodiimide (6.9 g, 33.6 mmol) and dimethylaminopyridine (0.2 g, 1.68 mmol) are added. The temperature is let reach the room value and the mixture is left under stirring for 24 hours. The precipitate is filtered and the organic phase is washed with water and extracted with chloroform. The organic phase is anhydri-fied with sodium sulphate and the solvent evaporated at reduced pressure. The raw product is purified by chromatography on silica gel eluting with methylene chloride/methanol 20/0.5 (v/v ratio). 1.3 g of 3-[(2-hydroxy) ethyloxy]propanoic acid 4-acetylamino phenyl ester are obtained. (Yield 33%)

¹H NMR (CDCl₃): 7.45 (2H, d); 7.02(2H, d); 4.40 (2H, t); 3.75 (6H,m); 2.14 (3H, s).

B) Preparation of 3-[(2-iodo)ethyloxy]propanoic acid 4-acetylamino phenyl ester

To a solution of 3-[(2-hydroxy)ethyloxy]propanoic acid 4-acetylamino phenyl ester (1.5 g, 5.6 mmol), imidazol (0.57 g, 8.4 mmol) and triphenylphosphine (1.9 g, 7.28 mmol) in ether (15 ml) and acetonitrile (10 ml) cooled at 0°C with ice bath, iodine (1.99 g, 7.84 mmol) is added and it is left under stirring at 0°C for 2 hours. Then the temperature is let reach the room value, hexane is added, the precipitate is filtered and the solvent is evaporated at reduced pressure. The raw product is purified by chromatography on silica gel eluting with hexane/ethyl acetate 3/7 (v/v ratio). 1 g of 3-[(2-iodo)ethyloxy]propanoic acid 4-acetylamino phenyl ester is obtained.

(Yield 48%)

^1H NMR (CDCl_3): 7.45 (2H, d); 7.02 (2H, d); 4.40 (2H, t); 3.75 (4H, t); 3.54 (2H, t); 2.14 (3H, s).

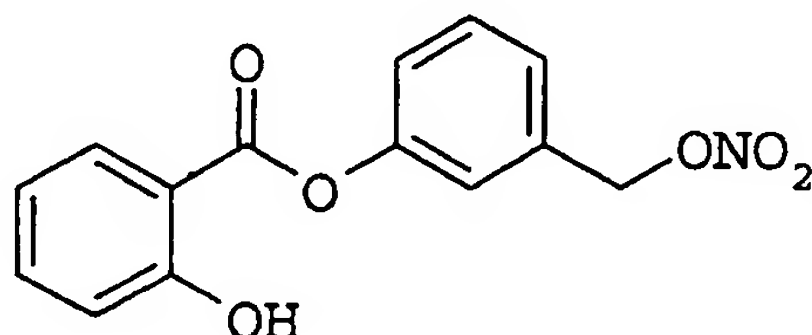
C) Preparation of 3-[(2-nitrooxy)ethyloxy]propanoic acid 4-acetylamino phenyl ester

To a solution of 3-[(2-iodo)ethyloxy]propanoic acid 4-acetylamino phenyl ester (1 g, 2.64 mmol) in acetonitrile (40 ml) silver nitrate (0.9 g, 5.28 mmol) is added. The reaction mixture is heated for 5 hours in absence of light at 60°C , then cooled to room temperature, filtered for removing the silver salts, and evaporated at reduced pressure. The residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 3/7 (v/v ratio). 0.46 g of 3-[(2-nitrooxy) ethyloxy]propanoic acid 4-acetylamino phenyl ester are obtained. (Yield 56%)

^1H NMR (CDCl_3): 7.45 (2H, d); 7.02 (2H, d); 4.58 (2H, t); 4.40 (2H, t); 3.75 (4H, t); 2.14 (3H, s).

EXAMPLE 15

Synthesis of 2-hydroxybenzoic acid 3-(nitrooxymethyl) phenyl ester



To a solution of 2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenylester (2 g, 6.04 mmol), obtained as described in Example 5, in tetrahydrofuran (10 ml), methanol (5 ml) and water (4 ml), imidazol (0.04 g, 0.6 mmol) is added. The mixture is left under stirring at room temperature for 20 days, then the solvent is evaporated at reduced pressure, the residue is treated with ethyl acetate and washed with water.

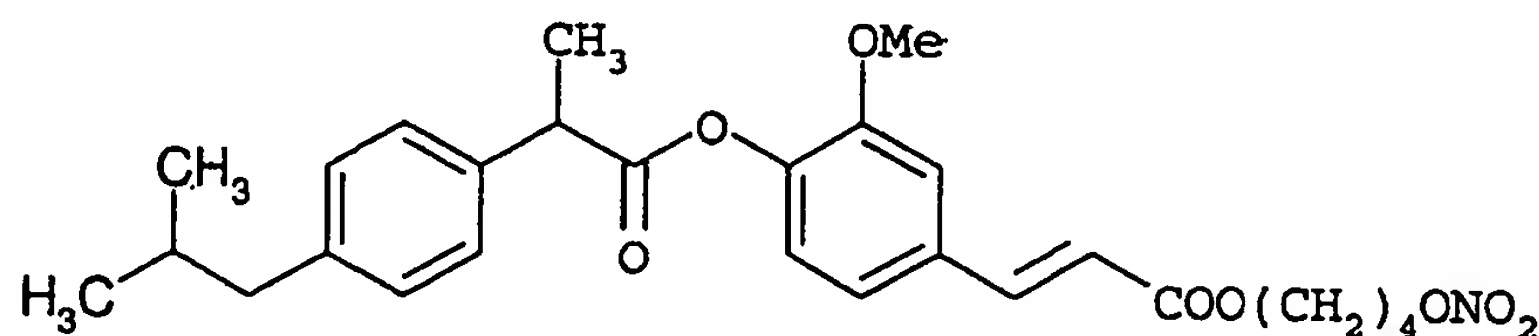
The organic phase is anhydriified with sodium sulphate and the solvent is evaporated at reduced pressure. The reaction raw product is purified by chromatography on silica gel using

as eluent hexane/ethyl acetate (9/1 v/v) to give 2-hydroxybenzoic acid 3-(nitrooxymethyl)phenylester (0.8 g). Yield 46%.

^1H NMR (CDCl_3): 10.46 (1H, s); 8.13 (1H, dd); 7.56 (2H, m); 7.34 (3H, m); 7.05 (2H, m); 5.51 (2H, s).

EXAMPLE 16

Synthesis of trans-3-[4-[α -methyl-[4-(-2-methylpropyl)benzene] acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-(nitrooxy) butyl ester having formula:



A) Synthesis of trans-3-[4-[α -methyl-[4-(-2-methylpropyl)benzene]acetyloxy]-3-methoxyphenyl]-2-propenoic acid

To a solution of α -methyl-[4-(2-methylpropyl)benzene]acetic acid (5.03 g, 24.4 mmol) in tetrahydrofuran (100 ml) and N,N-dimethylformamide (5 ml), 1,1-carbonyldiimidazole (4.25 g, 24.8 mmol) is added. After 1 hour the obtained solution is treated with ferulic acid (4.90 g, 25 mmol), sodium ethylate (89 mg) is added and it is left at room temperature under stirring for 12 hours. The reaction mixture is washed with HCl 5%, then with water and at last with brine. The organic phase is anhydriified with sodium sulphate and evaporated at reduced pressure.

The obtained residue is purified by chromatography on silica gel, eluting with ethyl acetate/n-hexane 7/3. 5.1 g of trans-3-[4-[α -methyl-[4-(-2-methylpropyl)benzene] acetyl]-3-methoxyphenyl]-2-propenoic acid are obtained as a white solid having m.p. 131-137°C.

^1H -NMR (CDCl_3) : 7.72 (1H, d), 7.32 (2H, dd), 7.26 (1H, m), 7.16-7.07 (4H, m), 6.98 (1H, d), 6.37 (1H, d), 3.99 (1H, q),

3.73 (3H, s), 2.47 (2H, d), 1.88 (1H, m), 1.63 (3H, d), 0.92 (6H, d).

B) Synthesis of trans-3-[4-[α -methyl-[4-(-2-methylpropyl)benzene]acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-bromobutyl ester

To a solution of trans-3-[4-[α -methyl-[4-(-2-methylpropyl)benzene]acetyloxy]-3-methoxyphenyl]-2-propenoic acid (5.33 g, 14 mmol) in N,N-dimethylformamide (130 ml), sodium ethylate (1.2 g, 16 mmol) is added under stirring. After 1 hour to the obtained mixture 1,4-dibromobutane (10 g, 46 mmol) is added and the mixture is let react at room temperature for 12 hours. The reaction mixture is washed with 5% HCl, then with water and at last with brine, the organic phase is anhydrified with sodium sulphate and evaporated at reduced pressure. The obtained residue is purified by chromatography on silica gel eluting with n-hexane/ethyl acetate 8/2. 4.46 g of trans-3-[4-hydroxy-[α -methyl-[4-(-2-methylpropyl)benzene]acetyl]-3-methoxyphenyl]-2-propenoyl 4-bromobutyl ester are obtained.

C) Synthesis of trans-3-[4-[α -methyl-[4-(-2-methylpropyl)benzene]acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-(nitrooxy) butyl ester

To a solution of trans-3-[4-[α -methyl-[4-(-2-methylpropyl)benzene]acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-bromobutyl ester (4 g, 7.72 mmol) in acetonitrile (70 ml) silver nitrate (2.58 g, 15 mmol) is added. The reaction mixture is heated under reflux for 2 hours sheltered from light. At the end the formed salt is removed by filtration and the solution is evaporated at reduced pressure. The recovered residue is purified by chromatography on silica gel, eluting with n-hexane/ethyl acetate 8/2. 2.4 g of trans-3-[4-[α -methyl-[4-(-2-methylpropyl)benzene]acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-(nitrooxy) butyl ester are obtained as oil.

$^1\text{H-NMR}$ (CDCl_3): 7.62 (1H, d), 7.32 (2H, d), 7.15 (2H, d), 7.16-7.05 (2H, m), 6.96 (1H, d), 6.35 (1H, d), 4.51 (2H, t), 4.24 (2H, t), 3.99 (1H, q), 3.74 (3H, s), 2.48 (2H, d), 1.89-1.83 (5H, m), 1.62 (3H, d), 0.92 (6H, d).

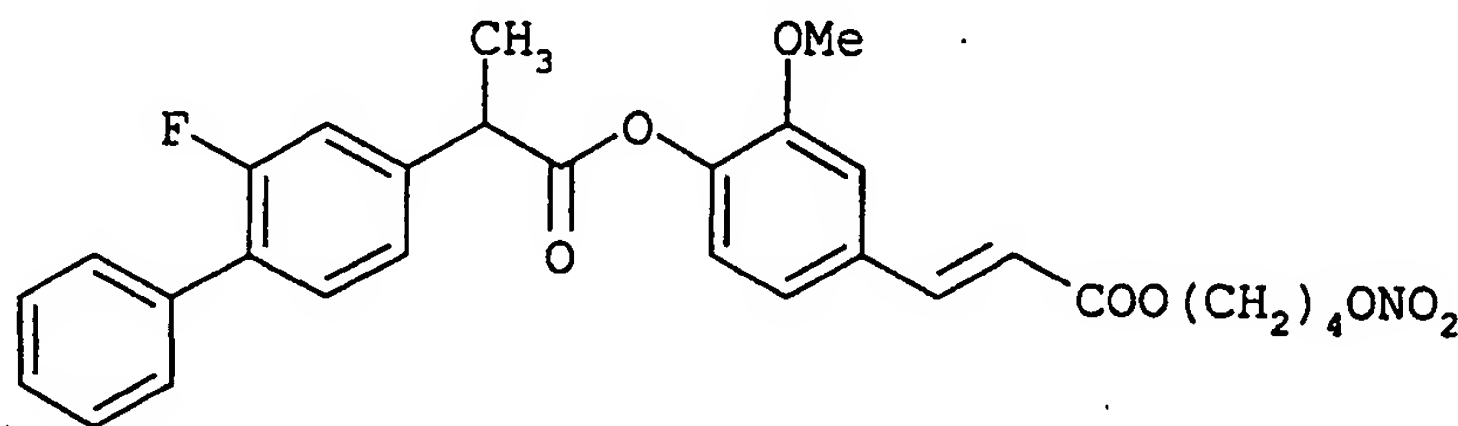
Elementary analysis:

Calculated C: 64.91% H: 6.66% N: 2.82%

Found C: 64.83% H: 6.52% N: 2.69%

EXAMPLE 17

Synthesis of trans-3-[4-[2-fluoro- α -methyl-(1,1'-biphenyl)-4-acetyloxy]-3-methoxyphenyl]-2-propenoyl 4-(nitrooxy) butyl ester having formula:



The compound is synthesized according to the process described in Example 16. The process total yield is 32%. The substance appears as an amorphous solid.

$^1\text{H-NMR}$ (CDCl_3): 7.40-7.25 (9H, m), 7.07-7.01 (2H, d), 6.98 (1H, m), 6.38 (1H, d), 4.44 (2H, t), 4.46 (2H, t), 4.21 (2H, t), 4.04 (1H, q), 3.73 (3H, s), 1.72 (4H, m), 1.65 (3H, d).

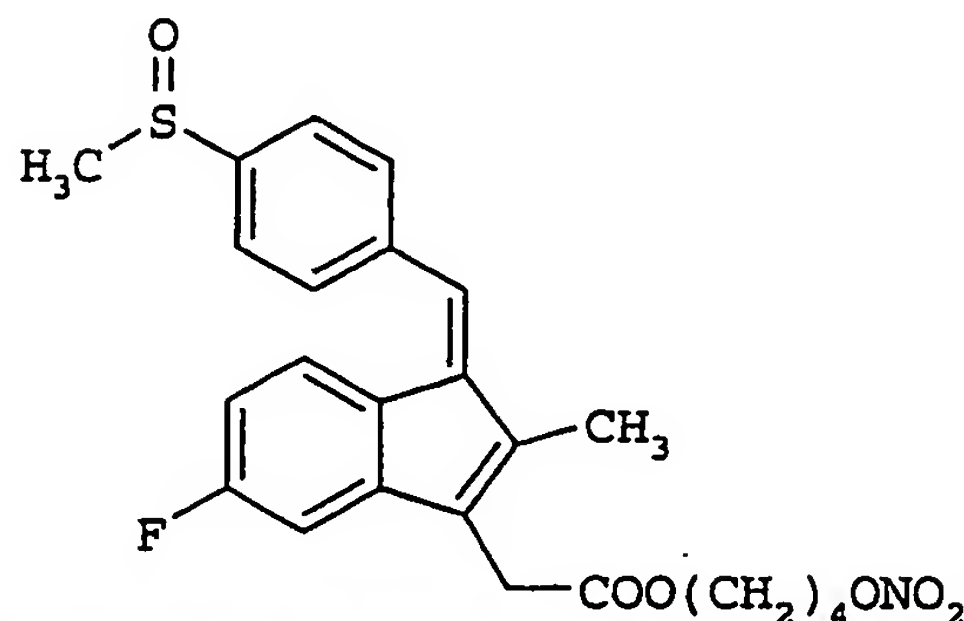
Elementary analysis:

Calculated C: 64.79% H: 5.25% N: 2.62% F: 3.53%

Found C: 64.85% H: 5.31% N: 2.74% F: 3.48%

EXAMPLE 18

Syntheis of (Z)-5-fluoro-2-methyl-1-[[4-(methylsulphinyl)phenyl]methylene]-1H-indene-3-acetic acid (4-nitrooxy)butyl ester



A) Synthesis of (Z)-5-fluoro-2-methyl-1-[[4-(methylsulphinyl)phenyl]methylene]-1H-indene-3-acetic acid 4-bromobutyl ester

To a solution of Sulindac (5.17 g, 14.5 mmoles) in dimethylformamide (50 ml) EtONa (1.18 g, 16.4 mmoles) is added. The reaction mixture is kept under stirring for one hour, then 1,4-dibromobutane dissolved in dimethylformamide (20 ml) is added.

The reaction mixture is kept under stirring at room temperature for 8 hours, ethyl acetate is added and the mixture is washed with water. The organic phase is anhydrified with sodium sulphate and the solvent is evaporated at reduced pressure.

The reaction raw product is purified by chromatography on silica gel eluting with a mixture of hexane/ethyl acetate (3/7 v/v). Cis-5-fluoro-2-methyl-1-[[4-(methylsulphinyl)phenyl]methylene]-1H-indene-3-acetic acid 4-bromobutyl ester (3.8 g) is obtained as a yellow solid. Yield 55%.

B) Synthesis of (Z)-5-fluoro-2-methyl-1-[[4-(methylsulphinyl)phenyl]methylene]-1H-indene-3-acetic acid (4-nitrooxy)butyl ester

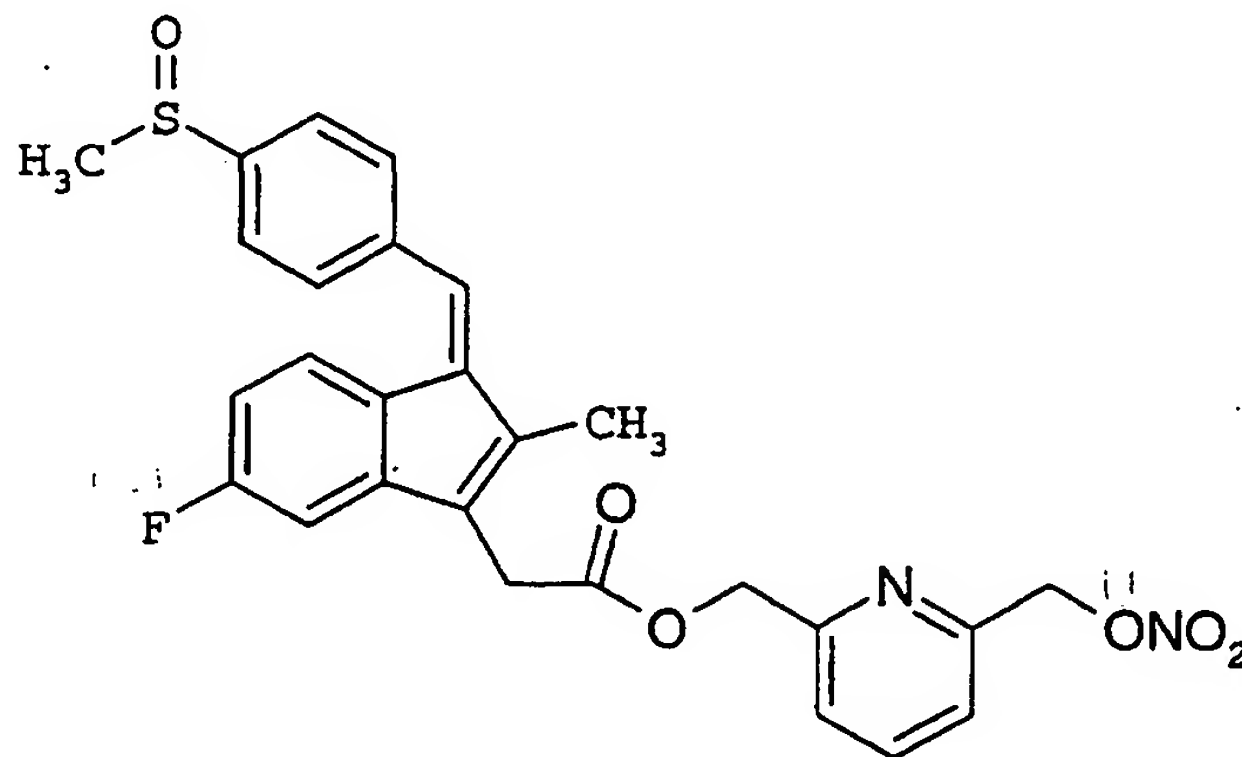
To a solution of cis-5-fluoro-2-methyl-1-[[4-(methylsulphinyl)phenyl]methylene]-1H-indene-3-acetic acid 4-bromo-

butyl ester (3.8 g, 7.7 mmol) in acetonitrile (50 ml) AgNO_3 (3.9 g, 22.3 mmol) is added sheltered from light. The mixture is heated at 80°C for 48 hours, then the precipitate is filtered and the solvent is evaporated. The reaction raw product is purified by chromatography on silica gel eluting with a mixture of hexane/ethyl acetate (1/9 v/v). (Z)-5-fluoro-2-methyl-1-[[4-(methylsulphanyl) phenyl]methylene]-1H-indene-3-acetic acid (4-nitrooxy)butyl ester (2.6 g) is obtained as a yellow solid. Yield 68%.

^1H NMR (CDCl_3): 7.78-7.62 (4H, m); 7.17 (2H, m); 6.88 (1H, dd); 6.60-6.50 (1H, m); 4.39 (2H, t); 4.16 (2H, t); 3.57 (2H, s); 2.79 (3H, s); 2.20 (3H, s); 1.79-1.61 (4H, m).

EXAMPLE 19

Synthesis of (Z)-5-fluoro-2-methyl-1-[[4-(methylsulphanyl) phenyl]methylene]-1H-indene-3-acetic acid 6(nitrooxymethyl)-2-methyl pyridinyl ester



The (Z)-5-fluoro-2-methyl-1-[[4-(methylsulphanyl)phenyl]methylene]-1H-indene-3-acetic acid 6(nitrooxymethyl)-2-methyl pyridinyl ester is synthesized according to the process described in Example 1, starting from (Z)-5-fluoro-2-methyl-1-[[4-(methylsulphanyl)phenyl]methylene]-1H-indene-3-acetic acid and 2,6-bis (chloromethyl)pyridine. Total yield of the process 20%.

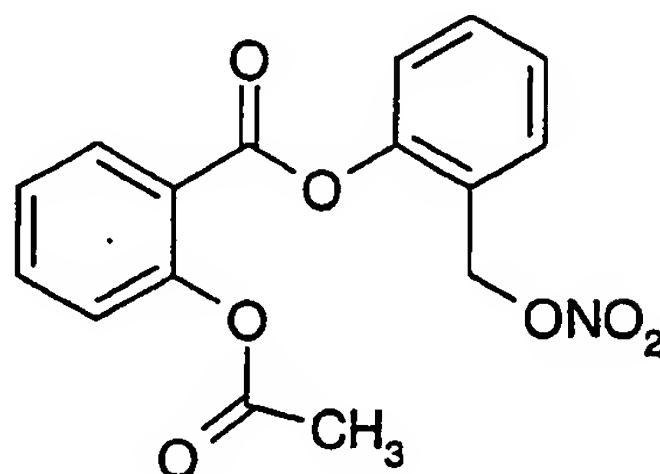
Elementary analysis:

Calculated C 57.09% N 5.12% F 3.47% Cl 6.48% S 5.86%

Found C 57.19% N 4.51% F 3.43% Cl 6.51% S 5.84%

EXAMPLE 20

Synthesis of 2-acetyloxybenzoic acid 2-(nitrooxymethyl)phenyl ester



The 2-acetyloxybenzoic acid 2-(nitrooxymethyl)phenyl ester is synthesized according to the process described in Example 6, starting from acetylsalicylic acid and 2-hydroxybenzaldehyde. Total yield of the process 68%.

¹H NMR (CDCl₃): 8.22 (1H, dd); 7.68 (1H, dt); 7.35 (6H, m); 5.40 (2H, s); 2.30 (3H, s).

PHARMACOLOGICAL EXAMPLES

EXAMPLE F1

Determination of the capability of the compounds of the invention to protect the animals from the liver injury induced by Concanavalin A.

The model in vivo used in the present example has been described in Tiegs G, Hentshel J, A Wendel. A T cell-dependent experimental liver injury in mice induced by Concanavalin A. J. Clin. Invest. 1992; 90:196-203.

The animals (rats of Swiss stock weighing about 20 g) are divided in groups of at least No. 10 animals for group. The animals receive concanavalin and solvent (treated control group), solvent (polyethylene glycol 400 - untreated control group), concanavalin and tested compound dissolved in the solvent (treated groups).

Rats are treated intravenously with concanavalin A (0.3 mg/rat), and after 5 minutes they receive by intraperitoneal injection the tested compounds, at the doses reported in Table 1, dissolved in polyethylenglycol 400.

Eight hours after the concanavalin A injection all the animals were sacrificed and the blood collected and examined. The data, reported in Table 1, are expressed as value of the plasmatic glutamic-pyruvic transaminase percentage of the animals treated with the tested compound with respect to the animals of the treated control group.

The results show that the compounds according to the invention protect from the liver injury induced by concanavalin A, while the native or precursor compounds even worsen the liver injury.

EXAMPLE F2

Determination of the antiproliferative activity of the compounds of the invention in cancerous cells.

Human adenocarcinoma (HT29) cells taken from colon affected by cancerous process were transferred into plates with 24 wells containing a cellular culture medium formed by 10% of foetal bovine serum, penicillin (50 U/ml), streptomycin (50 mg/ml) and PEG 400 (polyethylenglycol). After 24 hours a part of the plates is inoculated with the tested compounds dissolved in the carrier (PEG 400). 96 hours after the inoculation of the compounds the cellular growth was measured by haemocytometer. The results, reported in Table 2, are expressed as percentage of the cellular proliferation with respect to the controls.

The obtained results show that the compounds of the invention are much more effective in inhibiting the proliferation of the cancerous cells with respect to the corresponding native compounds.

EXAMPLE F3

Determination of the antiproliferative activity of the compounds of the invention in cancerous epithelial cells of bladder and prostate.

The experiment was carried out by using three human epithelial cellular lines of the prostate cancer (PNT1A; LLNcAP; PC3) and three human epithelial cellular lines of the bladder cancer (T24; 647V; 1207), the various types of cellular lines are identified on the basis of the characteristics, in particular of the aggressiveness, of the cancerous process.

The cancerous cells are sown, with an initial concentration of 20,000 cells/cm², in plates having 96 wells with a cellular culture medium RPMI added with foetal bovine serum 5% and L-Glutamine 1%. Solutions in dimethylsulphoxide of the tested compounds at three different concentrations (10⁻⁶ M; 10⁻⁵ M; 10⁻⁴ M) or the carrier (DMSO 1⁰/100) are added to the culture medium. 4 days after the treatment the cellular growth was measured by the method with MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) described by Turner in: Turner T., Chen P., Goodly L.J., Wells A. Clin. Exp. Metastasis 1996, 14, 409-418. The results, reported in Table 3, are expressed as inhibition percentage of the cellular proliferation determined by measuring the cellular proliferation in the cellular cultures treated with the tested compounds with respect to that measured in cellular cultures treated with dimethylsulphoxide 1⁰/100.

The results reported in Table 3 show that the nitrooxybutyl ester of sulindac (Ex. 18) at the 10⁻⁵ M concentration has a strong inhibitory effect on the proliferation of all kinds of cancerous cells examined; the compound of Ex. 16, reported in the Table with the simplified denomination of nitrooxybutyl ester of the ibuprofen der. with ferulic ac. and the compound of Ex. 17, reported in the Table

with the simplified denomination of nitrooxybutyl ester of the flurbiprofen der. with ferulic ac., are active in very aggressive prostate and bladder tumours, as it is shown by the results obtained on the cellular lines LNCaP and PC3, and 647V, 1207. The compound of Ex. 7, reported in the Table with the simplified denomination of nitrooxybutyl ester of the aspirin der. with ferulic ac. is active, at 10^{-5} concentrations, in prostate tumours as shown by the results obtained on the cellular lines LNCaP and PC3.

EXAMPLE F4

Determination in vitro of the effect of the compounds of the invention on the thymidine incorporation in human Adenocarcinoma HT29 cells.

Human adenocarcinoma cells are sown on plates having 24 wells (2.5×10^5 cells/plate) with a standard culture medium.

After 24 hours some plates are inoculated with the tested compounds dissolved in dimethylsulphoxide at a $200 \mu\text{M}$ concentration and others are treated with the tested compounds dissolved in dimethylsulphoxide at a $200 \mu\text{M}$ concentration in the presence of a solution of cisplatinum $25 \mu\text{M}$. After 15 hours of incubation the plates are put into contact with a solution of ^3H -thymidine $1 \mu\text{Ci/mol}$ (RAS. 3,000 Ci/mol).

The cell monolayer of each plate is first washed twice with a cold saline buffer, then treated with TCA (trichloroacetic acid) at 5% for 10 minutes and then washed three times with absolute alcohol. The cells of each well are dissolved in $500 \mu\text{l}$ of NaOH $0,1\text{N}$ and the incorporated radioactivity is determined by scintillation counting.

The obtained results are reported in Table 4 and expressed as percentage of ^3H -Thymidine incorporated in the cells treated with the tested compounds and in the presence of Cisplatinum, considering equal to 100 the amount of ^3H -

Timidine incorporated in the cells treated only with Cisplatinum.

Table 1

Activity in the prevention of the liver injury induced by Concavalin A		
Treatment	Dose (mg/kg)	Liver injury %
Treated controls	-	100
Untreated controls	-	2
Paracetamol	500	160
Nitrooxybutyl ester of the Paracetamol der. with ferulic acid (Ex. 8)	500	8
Paracetamol nitrooxybutyl ester (Ex. 9)	500	10
Aspirin	300	120
Aspirin ester with 5-nitrooxymethyl-2-hydroxymethyl pyridine (Ex. 3)	300	5
Aspirin ester with 3-nitrooxymethyl-2-hydroxymethyl pyridine (Ex. 4)	300	7
Sulindac	200	115
Ester sulindac with 6-nitrooxymethyl-2-hydroxymethyl pyridine (Ex. 19)	200	23
Sulindac 4-nitrooxybutyl ester (Ex. 18)	200	18

Table 2

Activity in vitro on the proliferation of cancerous cells		
Treatment	Concentration (μ M)	Proliferation %
Controls	-	100
Aspirin	500	100
Nitrooxybutyl ester of the aspirin der. with ferulic acid (Ex. 7)	300	50
Aspirin ester with 3- nitrooxymethylphenol (Ex. 5)	300	40
Aspirin ester with 4- nitrooxymethylphenol (Ex. 6)	10	0
Aspirin ester with 6- nitrooxymethyl-2-hydroxymethyl pyridine (Ex. 1)	10	0
Aspirin ester with 2- nitrooxymethylphenol (Ex. 20)	20	50
Sulindac	50	100
Sulindac 4-nitrooxybutyl ester (Ex. 18)	50	0

Table 3

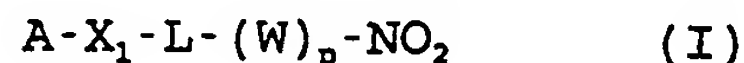
Determination in vitro of the inhibitory effect on the proliferation of cancerous human cells of prostate cancer and of bladder cancer of the compounds of the invention							
Compounds	Conc. (M)	Inhibition of the proliferative activity (%)					
		Human epithelial cells of prostate cancer			Human epithelial cells of bladder cancer		
		PNT1 A	LNCaP	PC3	T24	647V	1207
Sulindac Nitrooxybutyl ester (Ex. 18)	10^{-6}	3	17	5	0	9	0
	10^{-5}	38	74	68	82	80	74
	10^{-4}	81	88	74	93	92	88
Nitrooxybutyl ester of the Ibuprofen der. with Ferulic acid (Ex. 16)	10^{-6}	0	8	4	0	0	2
	10^{-5}	4	33	9	0	0	0
	10^{-4}	20	60	47	22	45	43
Nitrooxybutyl ester of the Flurbiprofen der. with Ferulic acid (Ex. 17)	10^{-6}	0	1	8	0	0	0
	10^{-5}	2	26	20	0	13	0
	10^{-4}	13	58	53	23	41	34
Nitrooxybutyl ester of the aspirin der. With Ferulic acid (Ex. 7)	10^{-6}	0	20	1	2	0	4
	10^{-5}	0	47	30	0	0	24
	10^{-4}	72	81	69	55	50	82

Table 4

Determination in vitro of the effect of some compounds on the thymidine incorporation in human adenocarcinoma cells			
Treatment	Conc. (μM)	Without Cisplatinium	With 25 μM Cisplatinium
Controls	-	438	100
Carrier (DMSO)	-	438	100
Salicylic acid Comparison	200	438	100
3-(nitrooxymethyl) phenyl ester of Salicylic acid (Ex.15)	200	246	50
Acetylsalicylic acid Comparison	200	438	100
3-(nitrooxymethyl) phenyl ester of Acetylsalicylic acid (Ex. 5)	200	192	46

CLAIMS

1. Use for preparing drugs for pre-cancer or cancer diseases on an inflammatory basis of nitroderivatives or salts thereof having the following general formula (I):

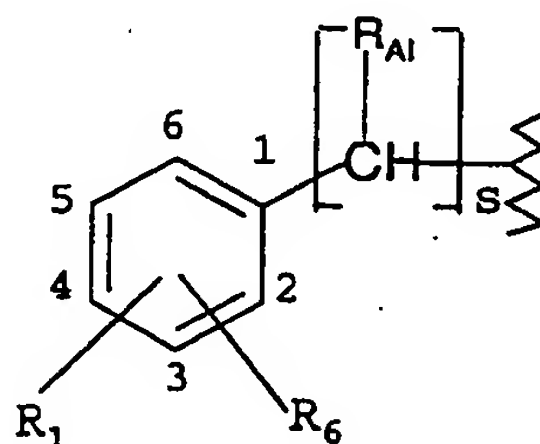


wherein:

p is an integer equal to 1 or 0;

A = R-T₁-, wherein

R is the radical of a precursor drug and it has the following formulas:



(AI)

wherein

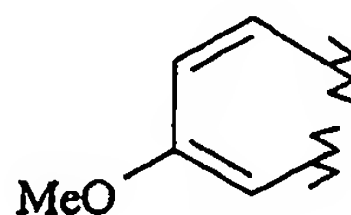
s is an integer and it is 1 or 0;

RAI is H, CH₃;

R₁ is OCOR₃, R₃ being a C₁-C₅ linear or branched radical, NHCOR₃, wherein R₃ has the above meaning, or R₁ is OH, CH₂CH(CH₃)₂, phenyl, benzoyl, 4,6-dichlorophenylamino;

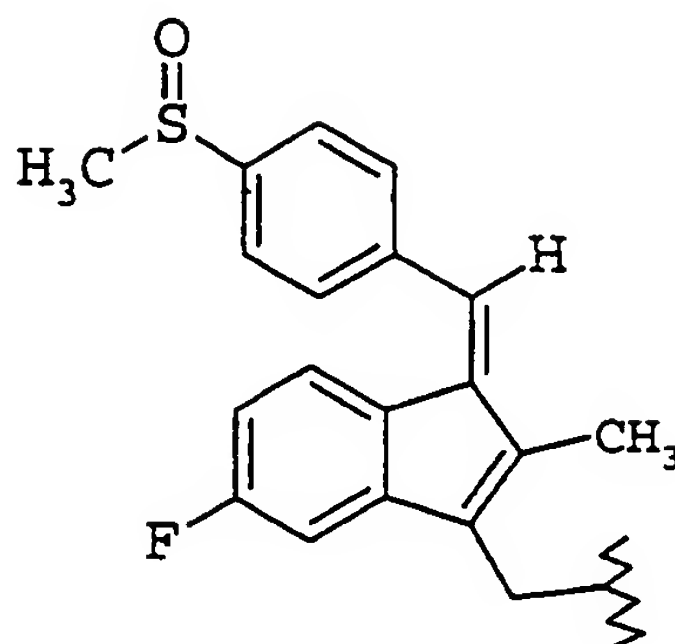
R₆ is H, or one halogen atom, preferably fluorine;

or R₁ and R₆, when are located in the adjacent positions 4 and 5 of the aromatic ring of formula (AI), form the radical of following formula (AIa):



(AIa)

or R can be the following formula:



(AII)

$T_1 = (CO)_t$ or $(X)_{t'}$, wherein $X = O, S, NR_{1c}, R_{1c}$ is H or a linear or branched alkyl, having from 1 to 5 carbon atoms, t and t' are integers and equal to zero or 1, with the proviso that $t = 1$ when $t' = 0$; $t = 0$ when $t' = 1$;

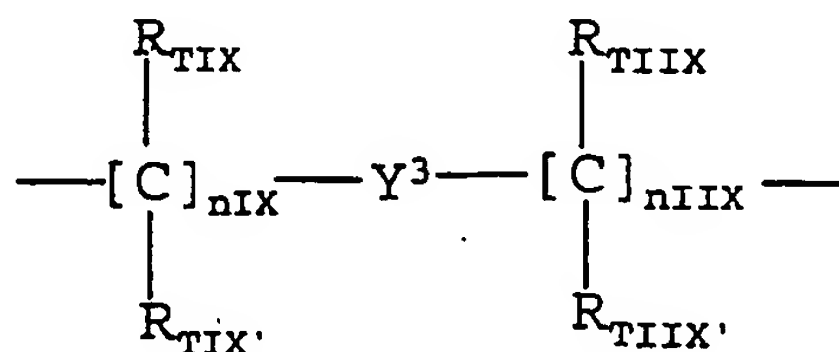
$X_1 = -T_B-Y-T_{BI}-$ wherein

T_B and T_{BI} are equal or different;

$T_B = (CO)$ when $t = 0$, $T_B = X$ when $t' = 0$, X being as above;

$T_{BI} = (CO)_{tx}$ or $(X)_{txx}$, wherein tx and txx have the value of 0 or 1; with the proviso that $tx = 1$ when $txx = 0$; and $tx = 0$ when $txx = 1$; X is as above;

Y is a bivalent linking group selected from the following:



(II)

wherein:

n_{IX} is an integer in the range 0-3, preferably

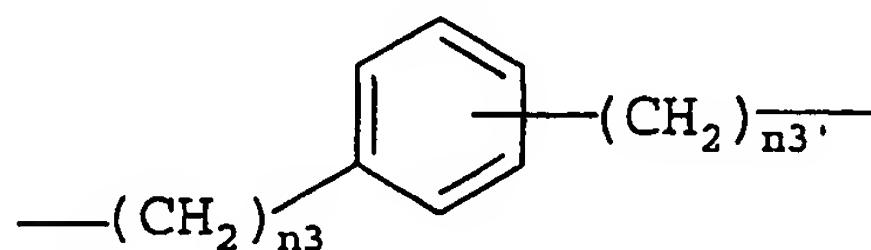
1;

n_{IIX} is an integer in the range 1-3, preferably 1;

R_{TIX} , $R_{TIX'}$, R_{TIIIX} , $R_{TIIIX'}$, equal to or different from each other are H or a C_1 - C_4 linear or branched alkyl; preferably R_{TIX} , $R_{TIX'}$, R_{TIIIX} , $R_{TIIIX'}$ are H;

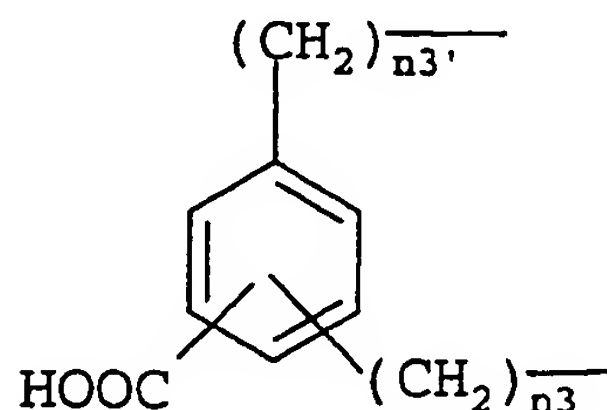
Y^3 is a saturated, unsaturated or aromatic heterocyclic ring, having 5 or 6 atoms, containing one or two nitrogen atoms,

- an alkylene group R' wherein R' is a C_1 - C_{20} linear or branched when possible, preferably having from 2 to 6 carbon atoms, optionally substituted with one or more of the following groups:
-NHCOR₃, wherein R_3 is as above, -NH₂, -OH or
- a cycloalkylene having from 5 to 7 carbon atoms, optionally substituted with side chains R' , R' being as above, one or more carbon atoms of the cycloalkylene ring can optionally be substituted by heteroatoms; or



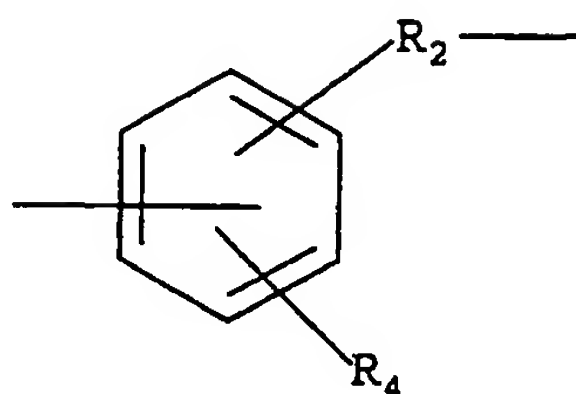
(III)

wherein $n3$ is an integer from 0 to 3 and $n3'$ is an integer from 1 to 3;



(IV)

wherein n_3 and n_3' have the above meaning,

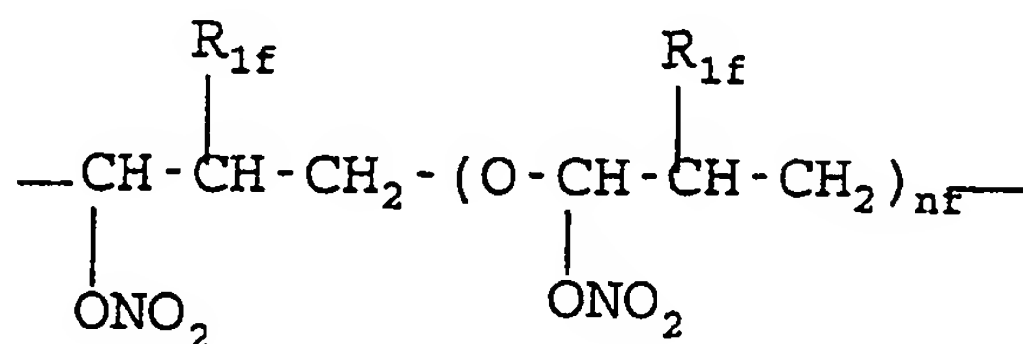


(V)

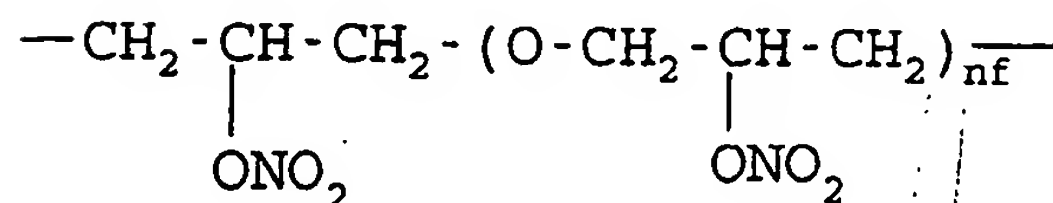
wherein

R_4 is hydroxy, hydrogen, R_5O - alkoxy wherein R_5 is a C_1 - C_{10} linear or branched or cyclic alkyl group, preferably R_5 is a methyl group;

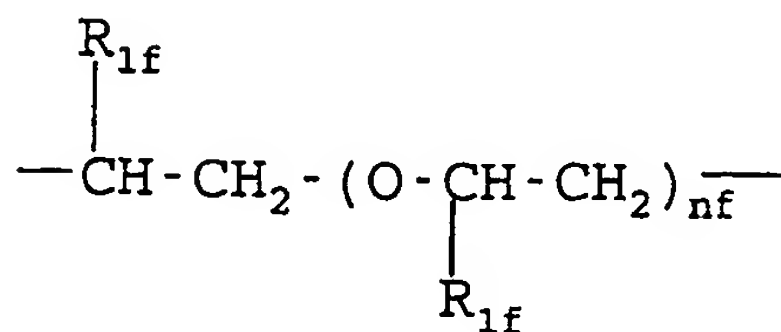
R_2 is a C_2 - C_{10} linear or branched alkenylene group which can contain one or more double bonds, preferably R_2 is the ethenylene group $(-CH=CH-)$; or



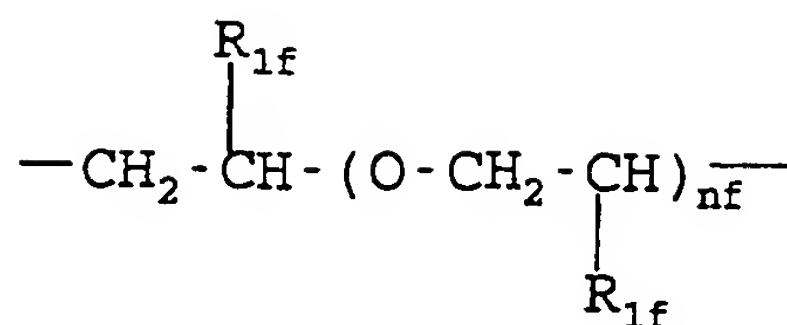
(VI)



(VII)



(VIII)



(IX)

wherein $\text{R}_{1f} = \text{H}$, CH_3 , and nf is an integer from 0 to 6; preferably from 0 to 4;

$\text{L} = \text{covalent bond}$, or $\text{L} = \text{X}$, X being as above, or $\text{L} = \text{CO}$;

$\text{W} = \text{Y}_t\text{O}$ wherein Y_t has the same meanings of Y and Y_t in the compound of formula (I) is equal to or different from Y .

2. Use according to claim 1, wherein the diseases on an inflammatory basis are those affecting the digestive apparatus, preferably the intestinal tract, such as colites, gastrites, enterites, duodenites; besides hepatopathies and tumoral processes related to diseases on an inflammatory basis.
3. Use according to claims 1-2, wherein:
 - when in formula (AI), R_1 is an acetyloxy group in position 2 of the ring, $s = 0$ and $\text{R}_6 = \text{H}$ and the free valence of the radical R is saturated with the $-\text{COOH}$ group, the compound is known as Acetylsalicylic Acid,
 - when in formula (AI) R_1 is a hydroxyl group in position 2 of the ring, $s = 0$ and $\text{R}_6 = \text{H}$ and the free valence of the radical R is saturated with a $-\text{COOH}$ group, the compound is known as Salicylic Acid,
 - when in formula (AI) R_1 is an acetylamino group in position 4 of the ring, $s = 0$ and $\text{R}_6 = \text{H}$ and the free valence is saturated with a $-\text{OH}$ group, the compound is known as Paracetamol,
 - when in formula (AI) R_1 is $\text{CH}_2\text{CH}(\text{CH}_3)_2$ in position 4 of the ring, $s = 1$, $\text{R}_{AI} = \text{CH}_3$ and $\text{R}_6 = \text{H}$ and the free valence is

saturated with a COOH group, the compound is known as Ibuprofen,

when in formula (AI) R_1 is phenyl and is in position 4 of the ring, $s = 1$, $R_{Ar} = CH_3$ and $R_6 = F$ in position 3 and the free valence is saturated with a -COOH group, the compound is known as Flurbiprofen,

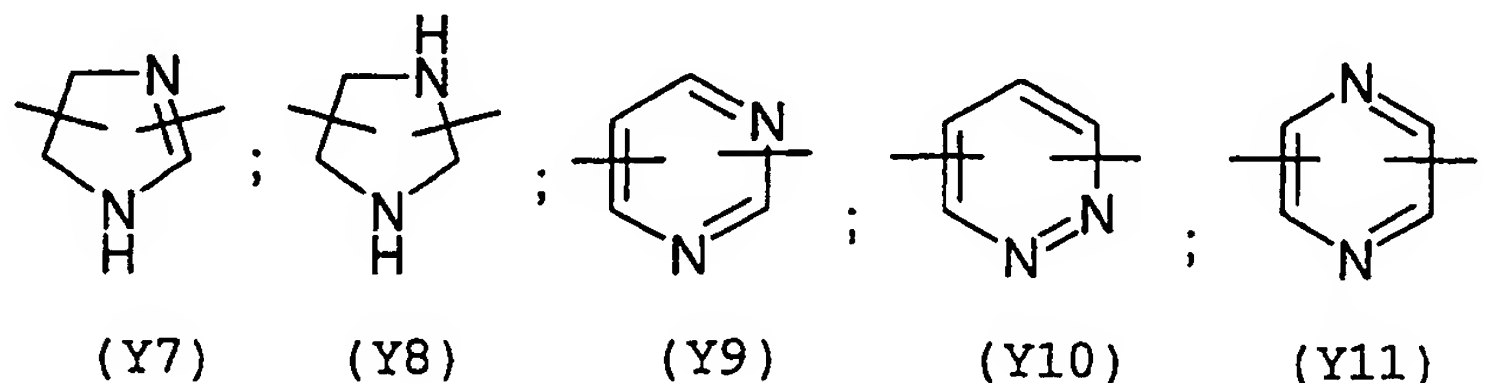
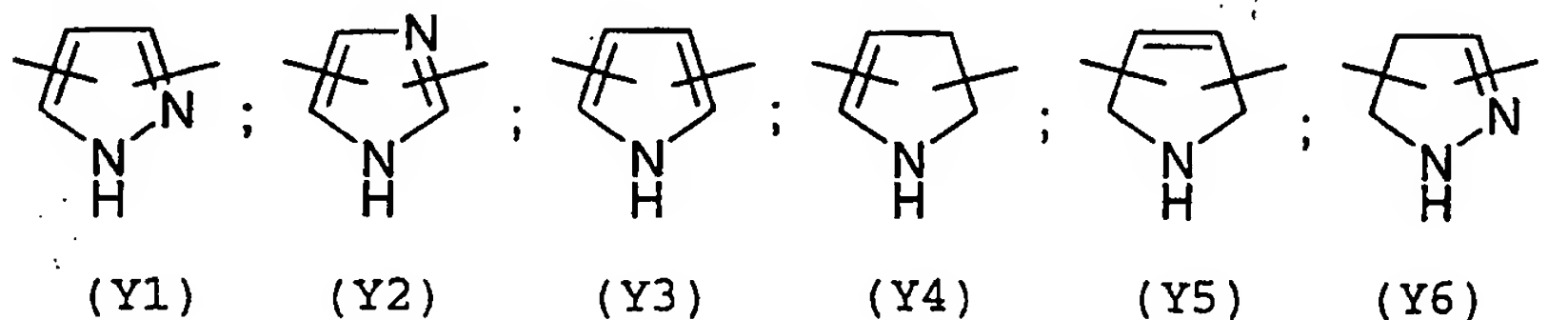
when in formula (AII) the free valence is saturated with the -COOH group, the compound is known as Sulindac,

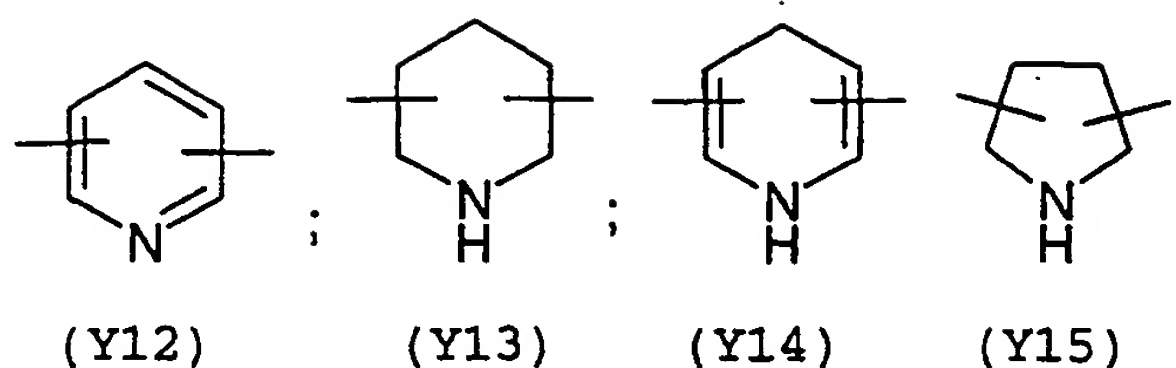
when in formula (AI) R_1 and R_6 are the radical of formula (AIa) and they are connected with the positions 4 and 5 of the ring, $s = 1$, $R_{Ar} = CH_3$, $R_6 = H$ and the free valence is saturated with a -COOH group, the compound is known as Naproxen,

when in formula (AI) R_1 is a benzoyl radical in position 5 of the aromatic ring, $s = 1$, $R_{Ar} = CH_3$, $R_6 = H$ and the free valence is saturated with a -COOH group, the compound is known as Ketoprofen,

when in formula (AI) $R_1 = 2,6$ -diclorofenilammino in position 2 of the ring, $s = 1$, $R_{Ar} = H$, $R_6 = H$ and the free valence is saturated with a -COOH group, the compound is known as Diclofenac.

4. Use according to claims 1-3, wherein Y^3 in formula (II) of the linking group Y of X_1 in formula (I) is selected from the following bivalent radicals:





5. Use according to claim 4, wherein Y^3 is an aromatic ring having 6 atoms, containing one nitrogen atom, said aromatic ring having the two free valences respectively in the positions 2 and 6, or 2 and 3 or 2 and 5 with respect to the heteroatom.
6. Use according to claims 4-5, wherein Y^3 is Y12 (pyridyl).
7. Use according to claims 1-6, wherein in formula (I):

- when in formula (AI) $s = 0$ and $R_6 = H$:
 - R is a radical of formula (AI) wherein the substituent R_1 is in position 2 of the aromatic ring, and it is selected between acetyloxy or hydroxyl, or it is an acetylamino group and then it is in position 4; $-T_1-T_8-$ is a $-CO-O-$ or $-O-OC-$ ester group; Y of the radical X_1 is a bivalent linking group selected from the following:
 - a radical of formula (III) as above, wherein, $n_3 = 0$ and $n_3' = 1$,
 - a radical of formula (II) as above wherein Y^3 is Y12 as above defined,
 - a radical of formula (VIII) as above wherein R_{1f} is hydrogen and $nf = 1$;
- $T_{B1} = -O-$, $L =$ covalent bond; $p = 0$;
- R is a radical of formula (AI) wherein the substituent R_1 is in position 2 of the aromatic ring, and it is selected between acetyloxy or hydroxyl, or it is an acetylamino group and then it is in position 4; $-T_1-T_8-$ is a $-CO-O-$ or $-O-OC-$ ester group; Y of the radical X_1 is a bivalent linking group having formula (V) as

above wherein R_4 is a methoxyl group and $R_2 = -CH=CH-$; $-T_{B1}-L-$ is a $-CO-O-$ or $-O-OC-$ ester group; $p = 1$; $W = YO$ wherein Y is $-(CH_2)_4-$ or $-(CH_2)_3-$;

- R is a radical of formula (AI) wherein the substituent R_1 is in position 4 of the aromatic ring, and it is acetylamino; $-T_1-T_B-$ = $-O-CO-$; Y of the radical X_1 is $-(CH_2)_3-$; $-T_{B1}-L-$ = $-O-$ (L = covalent bond); $p = 0$;
- R is a radical of formula (AI) wherein the substituent R_1 is in position 4 of the aromatic ring, and it is acetylamino; $-T_1-T_B-$ = $-O-CO-$; Y of the radical X_1 is an ethylene group substituted with an acetylamino group: $-CH(NHCOCH_3)-CH_2-$; $-T_{B1}-L-$ = $-S-CO-$; $p = 1$; $W = YO$ wherein Y is $-(CH_2)_3-$;

when in formula (AI) $s = 1$:

- R is a radical of formula (AI), $R_6 = H$ or F in position 3 of the ring, $R_1 = CH_2CH(CH_3)_2$ or phenyl in position 4, $-T_1-T_B-$ is a $-CO-O-$ ester group; Y of the radical X_1 is a bivalent linking group having formula (V) as above wherein R_4 is a methoxyl group and $R_2 = -CH=CH-$; $-T_{B1}-L-$ is a $-CO-O-$ ester group; $p = 1$; $W = YO$ wherein Y is $-(CH_2)_3-$;

- when in formula (I) R is a radical of formula (AII), $-T_1-T_B-$ = $-CO-O-$; Y of the radical X_1 is a bivalent linking group selected from the following:

- a radical of formula (II) as above wherein Y_3 is Y_{12} as above,
- $-(CH_2)_4-$;
- $-T_{B1}-$ = $-O-$, L = covalent bond; $p = 0$.

8. Use according to claims 1-7, wherein the compounds are selected from the following:

- when the drug radical has formula (AI) the compounds of formula (I) are the following:

2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)phenyl ester,
2-(hydroxy)benzoic acid 3-(nitrooxymethyl)phenyl ester,
2-(acetyloxy)benzoic acid 4-(nitrooxymethyl)phenyl ester,
2-(hydroxy)benzoic acid 4-(nitrooxymethyl)phenyl ester,
2-(acetyloxy)benzoic acid 2-(nitrooxymethyl)phenyl ester,
2-(hydroxy)benzoic acid 2-(nitrooxymethyl)phenyl ester,
2-(acetyloxy)benzoic acid 6-(nitrooxymethyl)-2-methyl
pyridinyl ester hydrochloride, or nitrate,
2-(hydroxy)benzoic acid 6-(nitrooxymethyl)-2-methyl
pyridinyl ester hydrochloride, or nitrate,
2-(acetyloxy)benzoic acid 5-(nitrooxymethyl)-2-methyl
pyridinyl ester hydrochloride, or nitrate,
2-(hydroxy)benzoic acid 5-(nitrooxymethyl)-2-methyl py-
ridinyl ester hydrochloride or nitrate,
2-(acetyloxy)benzoic acid 3-(nitrooxymethyl)-2-methyl
pyridinyl ester hydrochloride, or nitrate,
2-(hydroxy)benzoic acid 3-(nitrooxymethyl)-2-methyl py-
ridinyl ester hydrochloride, or nitrate,
trans-3-[4-[2-acetyloxybenzoyloxy]-3-methoxy phenyl]-2-
propenoic acid 4-(nitrooxy)butyl ester,
trans-3-[4-[2-hydroxybenzoyloxy]-3-methoxyphenyl]-2-
propenoic acid 4-(nitrooxy)butyl ester,
4-(nitrooxy)butanoic acid 4-(acetylamino)phenyl ester,
trans-3-[4-(4'-nitrooxybutyryloxy)-3-methoxy phenyl]-2-
propenoic acid 4-(acetylamino)phenyl ester,
3-(nitrooxymethyl)-benzoic acid 4-(acetylamino)phenyl
ester,
4-(nitrooxymethyl)-benzoic acid 4-(acetylamino)phenyl
ester,
2-(nitrooxymethyl)-benzoic acid 4-(acetylamino)phenyl
ester,

5-(nitrooxymethyl)pyridin-2-carboxylic acid 4-(acetyl amino)phenyl ester,
6-(nitrooxymethyl)-pyridin-2-carboxylic acid 4-(acetyl amino)phenyl ester,
3-(nitrooxymethyl)-pyridin-2-carboxylic acid 4-(acetyl amino)phenyl ester,
5-(nitrooxymethyl)-pyridin-2-carboxylic acid 4-(acetyl amino)phenyl ester,
5-(nitrooxymethyl)pyridin-2-acetic acid 4-(acetyl amino)phenyl ester,
6-(nitrooxymethyl)pyridin-2-acetic acid 4-(acetyl amino)phenyl ester,
3-(nitrooxymethyl)pyridin-2-acetic acid 4-(acetyl amino)phenyl ester,
3-[(2-nitrooxy)ethyloxy]propanoic acid 4-(acetyl amino)phenyl ester,
trans 3-[4-(4'-nitrooxybutyryloxy)-3-methoxy] phenyl-2-propenoic acid 4-(acetylamino)phenyl ester,
2-(acetylamino)-3-(4-nitrooxybutyryl)-3-mercapto propanoic acid 4-(acetylamino)phenyl ester,
trans-3-[4-[α -methyl-4-(2-methylpropyl)phenyl acetyloxy]-3-methoxyphenyl]-2-propenoic acid 4-nitrooxybutyl ester,
trans 3-[4-[2-fluoro- α -methyl(1,1'-biphenylyl)-acetyloxy]-3-methoxyphenyl]-2-propenoic acid 4-nitrooxy butyl ester,
(S) 6-metoxy- α -methyl-2-naphtalenacetic acid 2-methoxy-4-[(1E)-3-[4-(nitrooxy)butoxy]-3-oxo-1-propenyl]phenyl ester,
(S) 6-metoxy- α -methyl-2-naphtalenacetic acid 3-(nitrooxy methyl)phenyl ester,
(S) 6-metoxy- α -methyl-2-naphtalenacetic acid 6-(nitrooxy methyl)-2-methylpyridinyl ester,

(S,S)-N-acetyl-S-(6-methoxy- α -methyl-2-naphthaleneacetyl)
cysteine 4-(nitrooxy)butyl ester,
2-[(2,6-dichlorophenyl)amino]benzeneacetic acid 6-(nitro
oxymethyl)-2-methylpyridinyl ester chloridrate,

- when the drug radical has formula AII the compounds
of formula (I) are the following:

(Z)-5-fluoro-2-methyl-1-[[4-(methylsulphinyl)phenyl]
methylene]-1H-inden-3-acetic acid 4-(nitrooxy)butyl
ester,

(Z)-5-fluoro-2-methyl-1-[[4-(methylsulphinyl)phenyl]
methylene]-1H-inden-3-acetic acid 6-(nitrooxy-
methyl)-2-methyl pyridinyl ester hydrochloride, or
nitrate,

(Z)-5-fluoro-2-methyl-1-[[4-(methylsulphinyl)phenyl]
methylene]-1H-inden-3-acetic acid 5-(nitrooxy-
methyl)-2-methyl pyridinyl ester hydrochloride, or
nitrate,

(Z)-5-fluoro-2-methyl-1-[[4-(methylsulphinyl)phenyl]
methylene]-1H-inden-3-acetic acid 3-(nitrooxy-
methyl)-2-methyl pyridinyl ester hydrochloride, or
nitrate.

9. Use according to claims 1-8, wherein for the prevention
and/or treatment of tumoral diseases the compounds of
claims 1-8 are administered in combination with
chemotherapeutic drugs or in the radiotherapeutic
treatment.
10. Compounds according to claim 8.

INTERNATIONAL SEARCH REPORT

Inter. Application No

PCT/EP 01/11664

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C203/04 C07C233/54 C07C323/60 C07D201/02 C07C317/46
A61K31/21 C07D213/34 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 51988 A (NICOX SA ;DEL SOLDATO PIERO (IT); BENEDINI FRANCESCA (IT)) 8 September 2000 (2000-09-08)	1-10
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X	US 6 040 341 A (DEL SOLDATO PIERO ET AL) 21 March 2000 (2000-03-21)	1-3,8
Y	see examples and whole document	1-10
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8* document member of the same patent family

Date of the actual completion of the international search

1 March 2002

Date of mailing of the international search report

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Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

International Application No

PC/EP 01/11664

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	see the Tables 1-4 and the whole document	1-10
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P,X	WO 00 61541 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19) see page 2 and claim 1	1-10
X	WO 00 44705 A (NICOX SA ;DEL SOLDATO PIERO (IT); GARUFI MICHELE (IT)) 3 August 2000 (2000-08-03) see examples	1-3,8
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INTERNATIONAL SEARCH REPORT

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Inter al Application No

PC1/EP 01/11664

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		WO 0100563 A1	04-01-2001

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-2,4-7,9

Present claims 1-2,4-7,9 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the claims 3, 8 and 10 and the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



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PCT

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MI2000A 001848 8 August 2000 (08.08.2000) IT
- (71) Applicant (*for all designated States except US*): **NICOX S.A. [FR/FR]; 1900, rue des Crêtes, F-06560 Sophia Antipolis (FR).**
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I-20052 Monza (IT). BENE-DINI, Francesca [IT/IT]; Via Padova, 286, I-20100 Milano (IT).**
- (74) Agents: **SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni 2, I-20129 Milano (IT).**
- (81) Designated States (*national*): **AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA.**
- (84) Designated States (*regional*): **ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).**
- Published:**
— *without international search report and to be republished upon receipt of that report*
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: **DRUGS FOR INCONTINENCE**

(57) Abstract: Use in the incontinence of one or more of the following classes of drugs selected from the following: B) salified and non salified nitric oxide-donor drugs, of formula: A - X₁ - N(O)₂, B') nitrate salts of drugs used for the incontinence, and which do not contain in the molecule a nitric oxide donor group; C) organic or inorganic salts of compounds inhibiting phosphodiesterases.

WO 02/11707 A2

DRUGS FOR INCONTINENCE

* * * * *

The present invention relates to the use of classes of drugs, optionally mixtures thereof, for the urinary incontinence therapy.

More specifically, the invention relates to the use in the urinary incontinence therapy of one or more of the following compounds as defined hereunder, characterized in that they have a good efficacy in the urinary incontinence treatment combined with low side effects.

It is well known that the urinary incontinence can be considered a micturition control trouble consequent on a lesion or a dysfunction of the low urinary ducts. In particular the smooth musculature of the urinary bladder, called detrusor muscle, and the internal urethral sphincters (smooth musculature) and external (striated musculature) are involved. See for example Ferguson D. and Christopher N., Urinary Bladder Function and Drug Development, Trends in Pharmacological Sciences, 1996, 17, 161-165. In this publication it is mentioned that various kinds of incontinence exist characterized by different causes and symptoms. In particular it can be mentioned:

- incontinence from efforts which consists in the loss of small amounts of urine as a consequence of an intrabdominal pressure increase, due to, for example, a cough or an effort. It is due to the change of the vesico-urethral angle and to the musculature relaxation of the urethral sphincters. It is frequent above all in multipara women;
- incontinence from urgency which consists in the inability to control the bladder and it appears with a sudden and impelling stimulus to urinate. It is due to intermittent contractions of the bladder musculature without evident causes (detrusor instability) or consequent on interstitial cystitis or other inflammatory phenomena which cause bladder hyperexcitability. It seems that in all these cases alterations of the bladder innervation are present;

- incontinence from bladder overrelaxation which appears in the cases of chronic urinary retention due to obstructive causes. The bladder never empties itself completely with consequent continuous loss of small amounts of urine;
- total incontinence which consists in the complete lack of control on the bladder due to inability to control the sphincters. It is a consequence of serious neurological damages.

In the prior art the available therapies are based on three different approaches - see for example the above article and Anderson K.E., Pharmacology of Lower Urinary Tract Smooth Muscles and Penile Erectile Tissues, Pharmacological Reviews, 1993, 45, 253-308:

- reduction of the detrusor activity,
- modification of the sensory nervous transmission,
- modification of the urethral resistances.

According to the first approach, the detrusor contraction is stimulated by the parasympathetic system and acetylcholine is the main mediator. Therefore to reduce the bladder hyperactivity anticholinergic drugs are used which are effective but of limited use owing to the anticholinergic activity at systemic level. Indeed they cause side effects such as for example fauces dryness, constipation and tachycardia. If one considers that the bladder irritability is often associated to obstructive bladder pathologies, the administration of anticholinergic drugs can potentially cause crises of acute urinary retention.

For example anticholinergic drugs such as oxybutynin or tolterodine are quite effective. Their use is however limited by the side effects typical of anticholinergic agents (fauces dryness, dimmed sight, etc.) Occasionally patients under treatment with said products can also have cardiac rhythm troubles. In patients affected by glaucoma, a worsening of the pathology can happen, furthermore in old patients with prostatic hypertrophy a worsening of the urinary retention can take place.

Another pharmacological approach for reducing the detrusor activity considers the use of drugs which facilitate the opening of the channels of potassium, of calcium antagonists and of relaxing drugs of the smooth musculature.

Also in this case there are side effects, such as for example the arising of a marked hypotensive action due to the aspecific effect of vasodilation induced by these drugs.

The administration of β -agonist drugs induces an increase of the bladder capacity, but their use is limited by the serious side effects affecting the cardiovascular system.

A further pharmacological approach for reducing the bladder hyperactivity is the use of antidepressant drugs, but also with these therapeutic aids there are serious side effects affecting the cardiovascular system (orthostatic hypotension, arrhythmia).

Another pharmacological method for reducing the detrusor activity consists in the use of the prostglandin synthesis inhibitors which have been experimented in some cases of detrusor hyperactivity and enuresis with promising results. Also in this case the side effects which have been noticed have been significant. The use of these drugs is based on the fact that several prostglandines are synthesized at bladder level as a consequence of nervous stimulation and some of them would have the function of mediators of the detrusor muscle contractions. Some prostglandines would be furthermore involved in phenomena of incontinence from urgency and bladder hyperactivity noticed during some inflammatory pathologies of the urinary tract.

The non steroidal antiinflammatory drugs are potentially useful for reducing the limit of excitability of the urinary bladder, and are therefore effective in the cases of detrusor instability. Unfortunately they show the drawback that at active doses they are poorly tolerated especially at the gastrointestinal apparatus level.

The NO enzyme synthetase inhibitors could prevent the bladder hyperexcitability and hyperalgesia consequent on inflammatory phenomena such as interstitial cystitis; see Rice A.S.C., Topical Spinal Administration of a Nitric Oxide Synthase Inibitor Prevents the Hyper-Reflexia Associated with a Rat Model of Persistent Visceral Pain, Neuroscience Letters, 1995, 187, 111-114. However, at present, therapeutically usable drugs of this kind do not exist because of the corresponding aspecificity of their pharmacological profile.

The second approach which consists in the modification of the sensory nervous transmission (in the cases when the urinary incontinence derives from lesions of the nervous system) implies the use of active drugs on the neurotransmission, for example of gamma-aminobutyric acid (GABA), or peptides, or purines, which are important neurotransmitters at the urinary ducts level.

Also clinical studies which use capsaicin by intravesical instillation with sometimes positive results are known. However this treatment has limited clinical applications due to its transitory effect and besides obtainable only by local administration.

The third approach is based on the fact that at the urethra level the musculature tone is mediated by different neurotransmission systems, for example the adrenergic one by stimulation of the α receptors. To modify the urethral resistances α -agonist drugs are used with sometimes satisfactory results; they increase the pressure bearable by the urethra. However the use of these compounds is contraindicated in the case of obstructive pathologies of the bladder, in which even alpha-antagonist drugs are used. In these cases it is indeed frequent that an hyperactivity of the sphincters takes place, which hinders the regular bladder emptying, causing incontinence from urgency. Also in this case, as well as in the first above described approach, serious side effects of hypotensive type bound to the α -antagonist activity affecting the cardiocirculatory apparatus level are to be pointed out.

Up to now the commercially available drugs solve the problem only in a limited number of cases but generally inducing side effects also of a certain seriousness.

Good results have been obtained with products described in patent application WO 98/09948 in the name of the Applicant wherein nitroxyderivatives of particular classes of non steroidal antinflammatory drugs are used. These products are very good drugs for the incontinence treatment with low side effects, however they have the drawback to have to be mainly administered by os. When a parenteral administration is necessary (cases of bad absorption, seriously ill hospitalized patients where the administration by os cannot

be carried out), it has been found that the products mentioned in said application are not administrable by parenteral route.

The Applicant has unexpectedly and surprisingly found compounds effective in the incontinence treatment and giving lower side effects, and are administrable also parenterally, therefore overcoming the drawbacks of the prior art.

An object of the present invention is the use in the incontinence of one or more of the following classes of drugs selected from the following:

- A) nitric oxide donor drugs, optionally salified, of formula:



wherein A, X_1 , Z have the meaning defined below;

- B') nitrate salts of drugs used for the incontinence and which do not contain in the molecule a nitric oxide donor group;
- C) organic or inorganic salts of compounds inhibiting phosphodiesterases;

in the compounds of general formula:

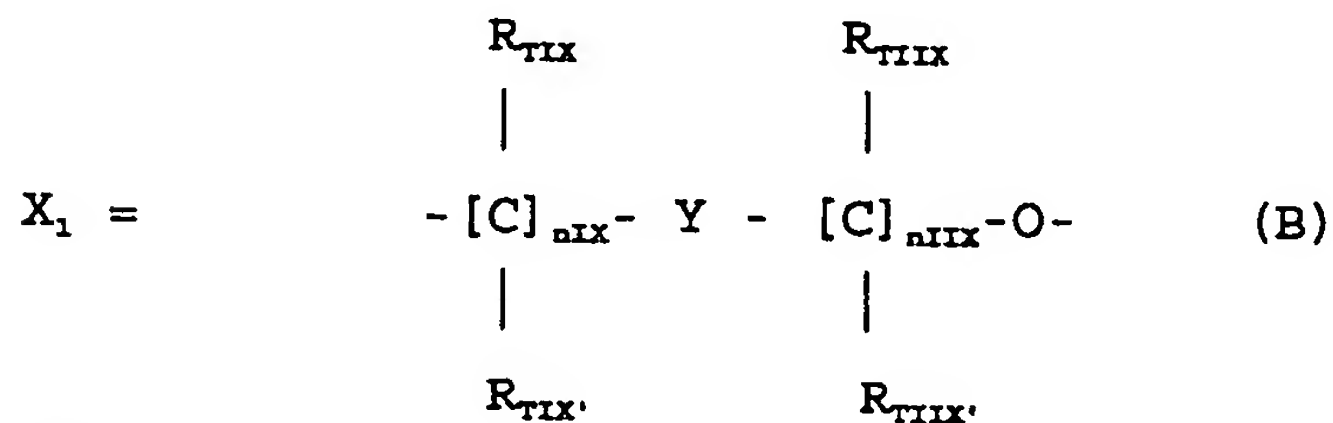


z is an integer and is 1 or 2, preferably 2;

A = $R(COX_u)_t$ and wherein t is an integer 0 or 1; u is 0 or 1;

X = O, NH, NR_{1c} wherein R_{1c} is a linear or branched C_1 - C_{10} alkyl;

X_1 is the following bivalent linking group:



wherein:

nIX is an integer in the range 0-3, preferably 1;

nIIX is an integer in the range 1-3, preferably 1;

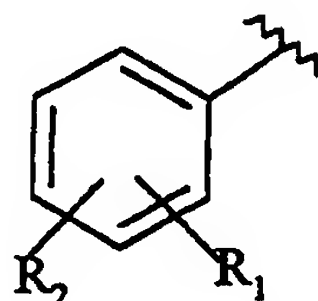
R_{TIX} , $R_{TIX'}$, R_{TIIIX} , $R_{TIIIX'}$, equal to or different from each other are H or linear or branched C_1 - C_4 alkyl; preferably R_{TIX} , $R_{TIX'}$, R_{TIIIX} , $R_{TIIIX'}$ are H;

Y is a heterocyclic ring containing one or two nitrogen atoms, optionally one oxygen or sulphur atom, said saturated, unsaturated or aromatic ring, having 5 or 6 atoms;

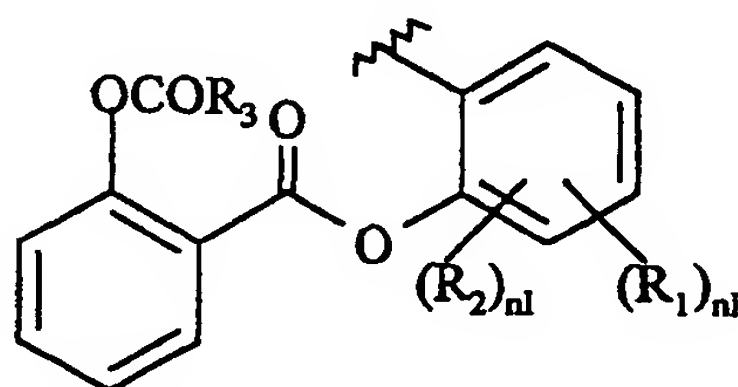
R is selected from the following groups:

Group I) wherein $t = 1$ and $u = 1$

Ia)



Ib)



wherein:

R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or linear or branched C_3 - C_5 alkyl, or the residue of a heterocycle with only one ring having 5 or 6 atoms which can be aromatic, partially or totally hydrogenated, containing one or more heteroatoms independently selected from O, N and S;

R_2 is hydrogen, hydroxy, halogen, linear or branched when possible C_1 - C_4 alkyl; a linear or branched when possible C_1 - C_4 alkoxy; a linear or branched when possible C_1 - C_4 perfluoroalkyl, for example trifluoromethyl; nitro, amino, mono- or di- (C_{1-4}) alkylamino;

nI is an integer 0 or 1;

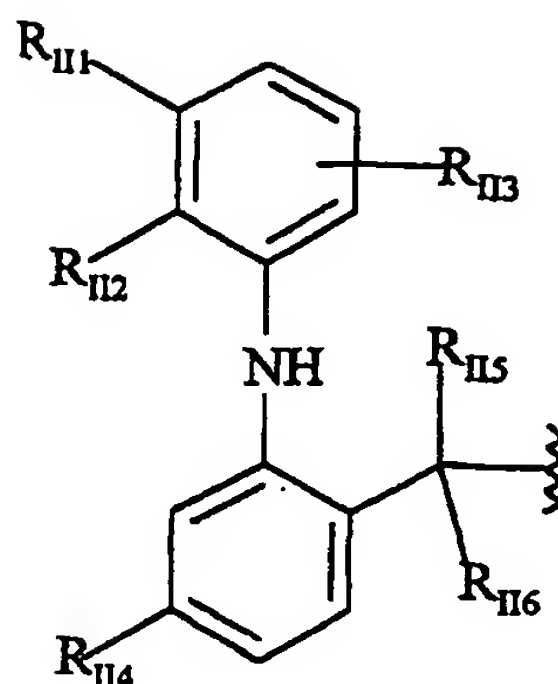
preferably in the compounds of formula Ia) X is equal to O or NH, R_1 is acetoxy, preferably in ortho position with respect to $-CO-$, R_2 is hydrogen; preferably X_1 is the linking group

(B) wherein $R_{TIX} = R_{TIX} = R_{TIX} = R_{TIX} = H$, $n_{IX} = n_{IX} = 1$;

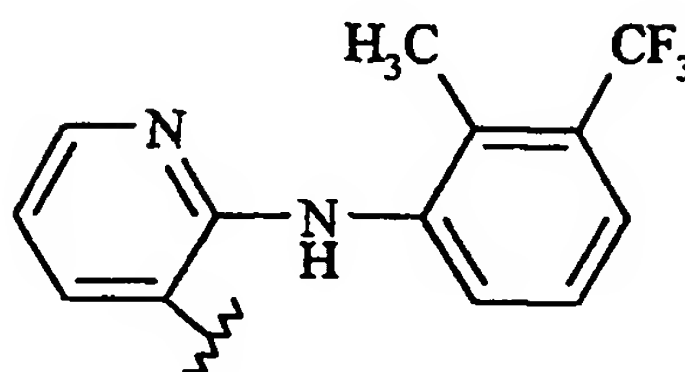
Preferably in the compounds of formula Ib) $R_3 = CH_3$, $nI = 0$, X is equal to O, X_1 is as above defined for Ia); in this case Ib) is the residue of the acetylsalicylsalicylic acid;

Group II, wherein $t = 1$, $u = 1$

IIa)



IIb)



wherein:

R_{II5} is H, linear or branched when possible C_1-C_3 alkyl;

R_{II6} has the same meaning as R_{II5} , or when R_{II5} is H it can be benzyl;

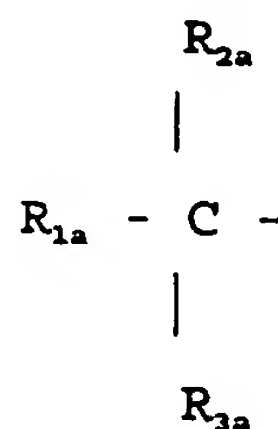
R_{II1} , R_{II2} and R_{II3} can independently be hydrogen, linear or branched when possible C_1-C_6 alkyl, or linear or branched when possible C_1-C_6 alkoxy, or Cl, F, Br;

R_{II4} is R_{II1} or bromine;

the compounds wherein R_{II1} , R_{II4} are hydrogen and R_{II2} and R_{II3} are chlorine in ortho position with respect to NH are preferred; R_{II5} and R_{II6} are H, X is equal to O, and X_1 is as above defined for the compounds of formula Ia);

IIb) is the residue of the 2-[(2-methyl-3-(trifluoromethyl)phenyl]amino]-3-pyridincarboxylic acid and when the -COOH group is present the compound is known as flunixin;

Group III) wherein $t = 1$, $u = 1$ and R is

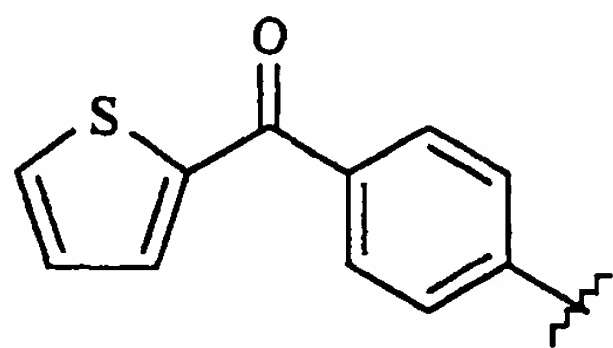


wherein:

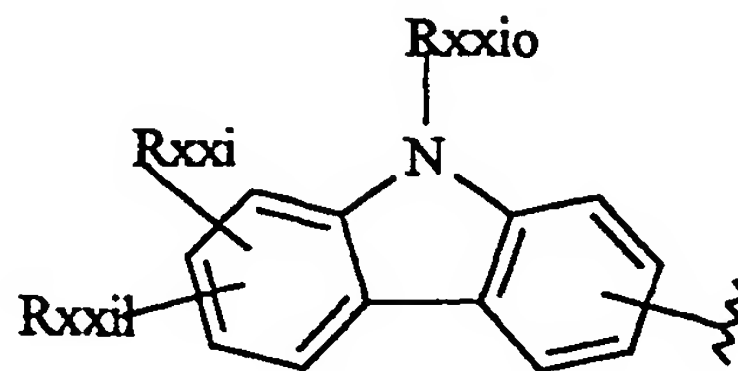
R_{2a} and R_{3a} are H, linear or branched when possible, substituted or not, C_1 - C_{12} alkyl or allyl, with the proviso that if one of the two is allyl, the other is H; preferably

R_{2a} is H, C_1 - C_4 alkyl, R_{3a} is H;

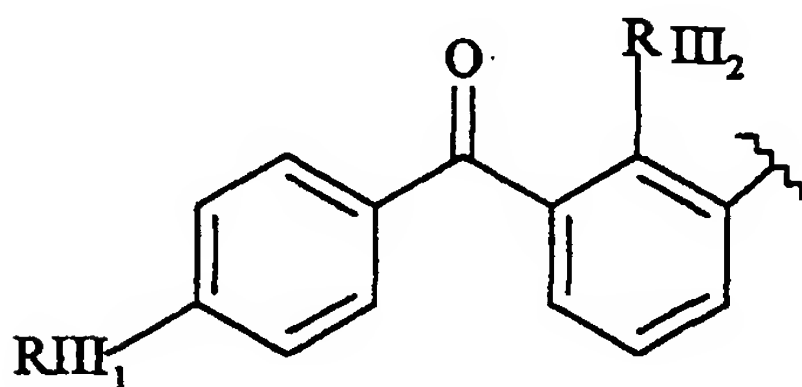
R_{1a} is selected from



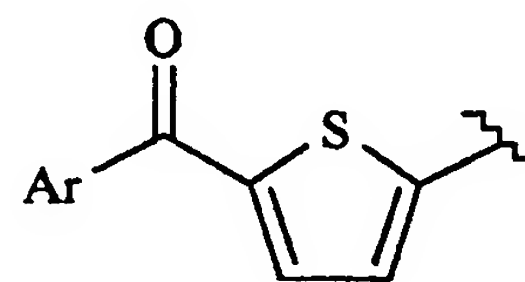
(II)



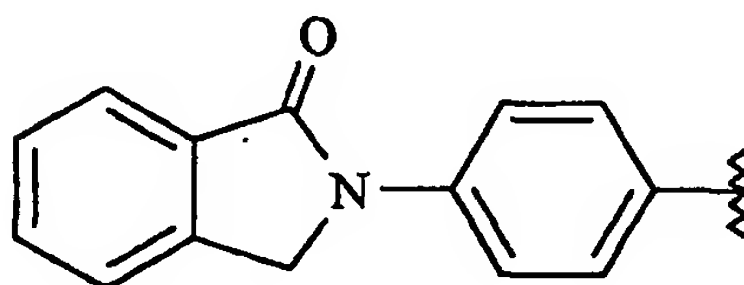
(XXI)



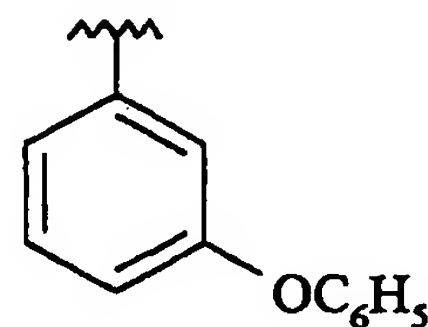
(IV)



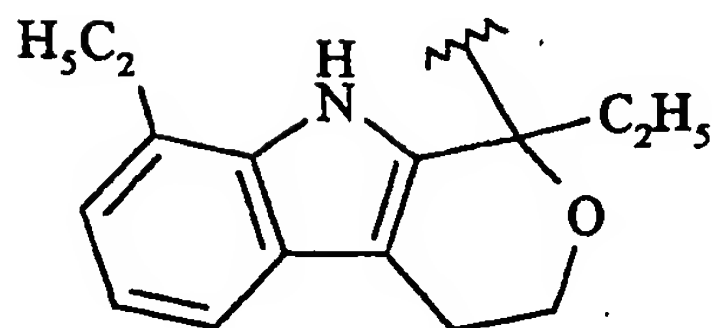
(XXXV)



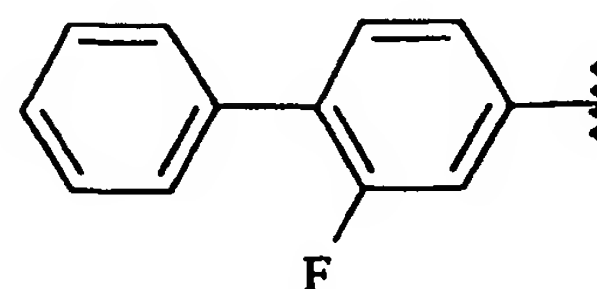
(VI)



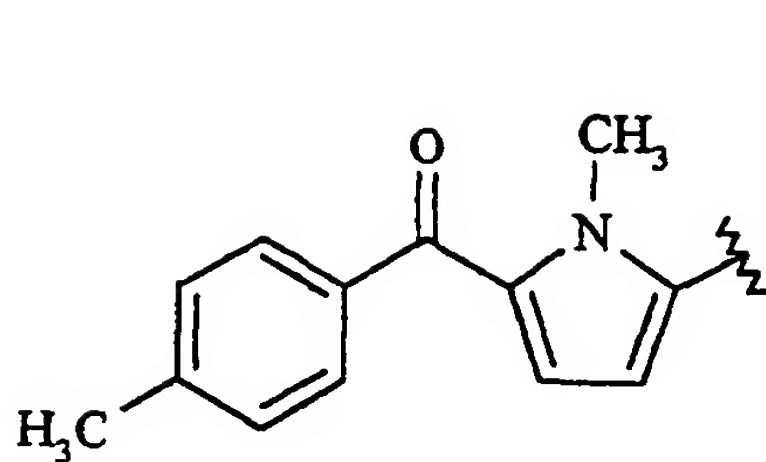
(VII)



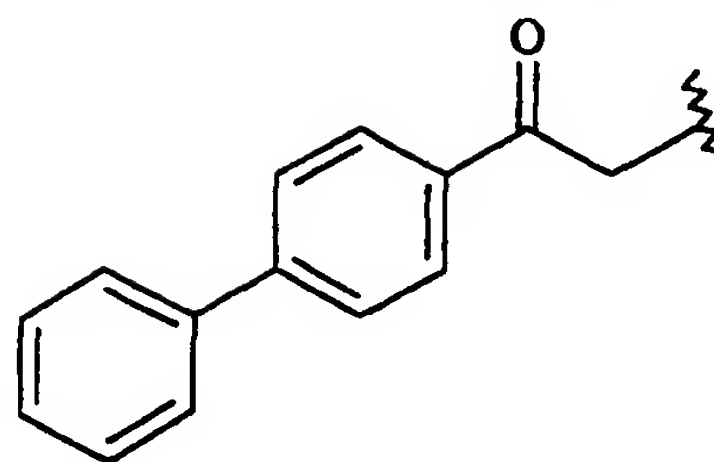
(VIII)



(IX)

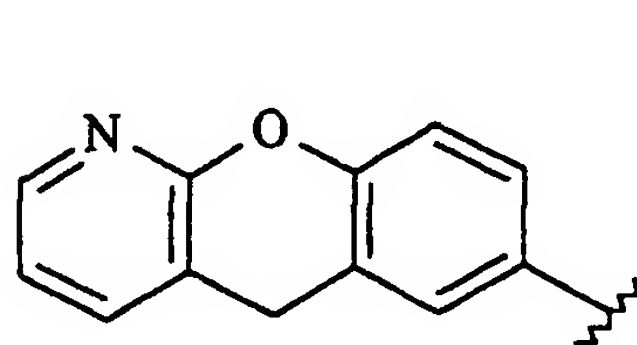


(X)

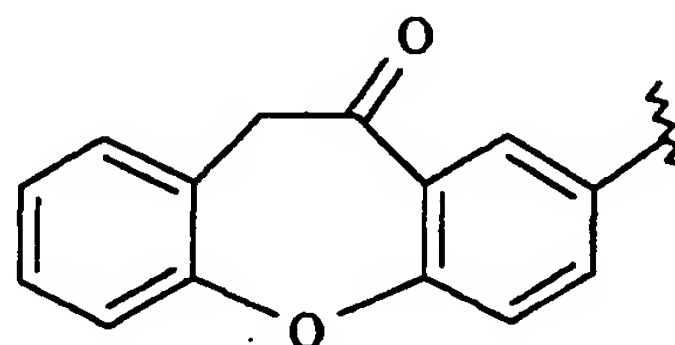


(III)

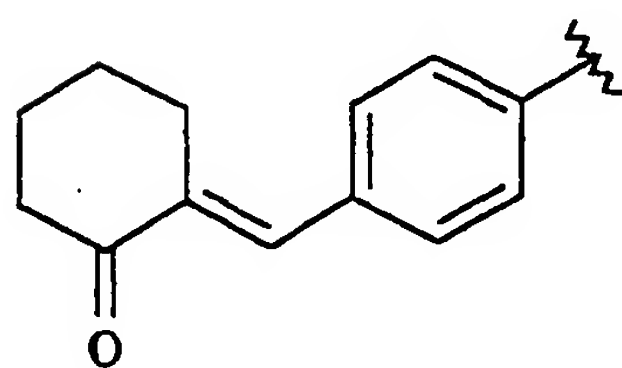
IIID) R_{1a} corresponds to the following formulas:



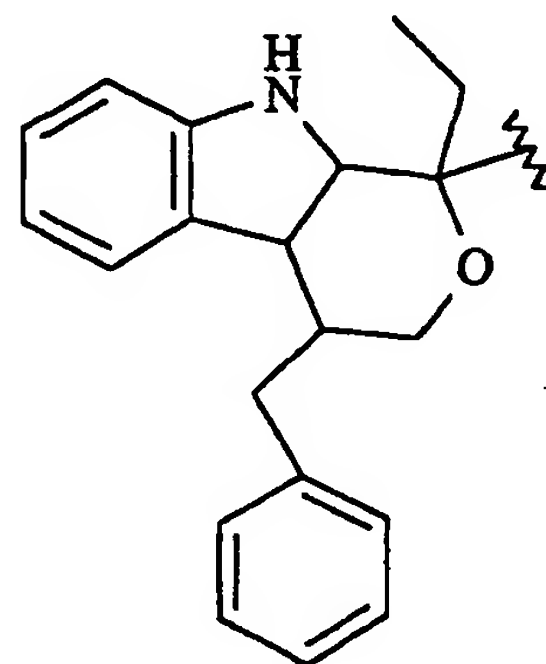
(IIIa)



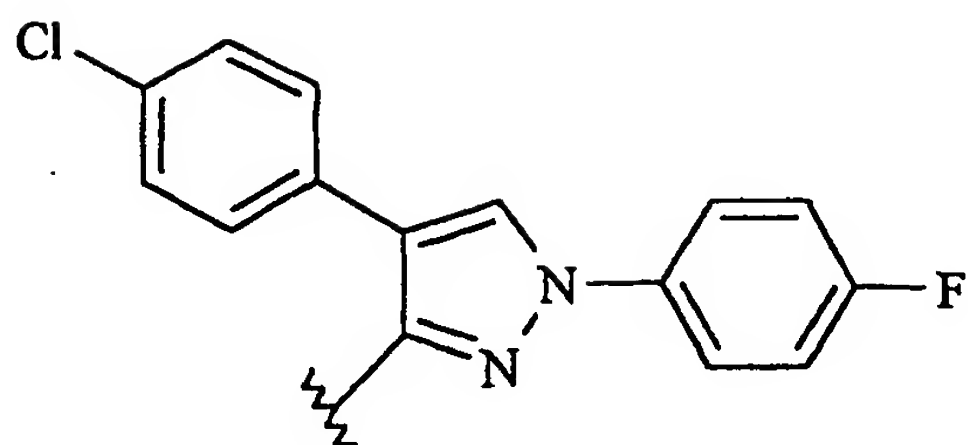
(XXX)



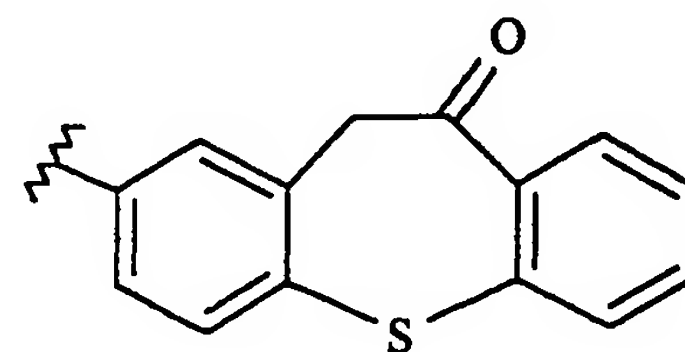
(XXXI)



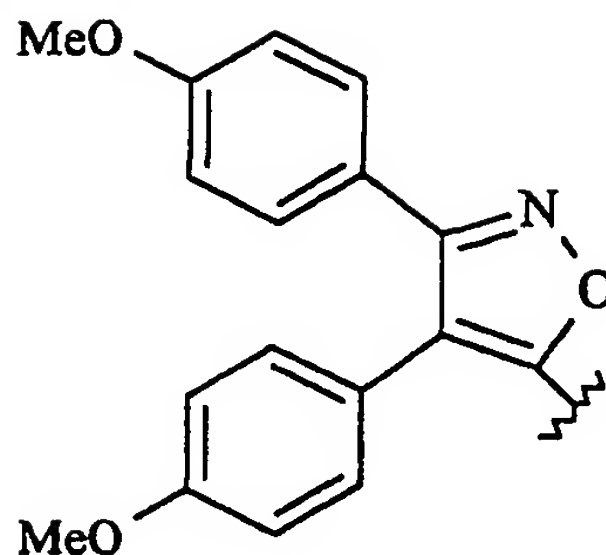
(XXXII)



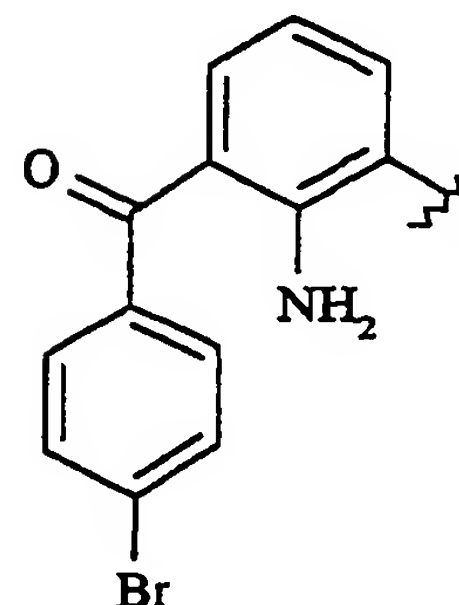
(XXXIII)



(XXXVI)



(XXXVII)



(XII)

wherein the meanings are the following:

- when R_{1a} is as defined in formula (IV), Ketoprofen residue:

R_{III1} is H, SR_{III3} wherein R_{III3} contains from 1 to 4 carbon atoms, linear or branched when possible;

R_{III2} is H, hydroxy;

the compounds wherein R_{III1} and R_{III2} are H, R_{3a} is H, and R_{2a} is methyl, $X = O$, are preferred;

- when R_{1a} is as defined in formula (XXI), carprofen residue:

R_{xx10} is H, linear or branched when possible alkyl from 1 to 6 carbon atoms, C_1-C_6 alkoxy carbonyl linked to a C_1-C_6 alkyl, C_1-C_6 carboxyalkyl, C_1-C_6 alkanoyl, optionally substituted with halogens, benzyl or halobenzyl, benzoyl or halobenzoyl;

R_{xx1} is H, halogen, hydroxy, CN, C_1-C_6 alkyl optionally containing OH groups, C_1-C_6 alkoxy, acetyl, benzyloxy, SR_{xx12} wherein R_{xx12} is C_1-C_6 alkyl; C_1-C_3 perfluoroalkyl; C_1-C_6 carboxyalkyl optionally containing OH groups, NO_2 , amino; sulphamoyl, di-alkyl sulphamoyl with C_1-C_6 alkyl, or difluoroalkylsulphonyl with C_1-C_3 alkyl;

R_{xx11} is halogen, CN, C_1-C_6 alkyl containing one or more OH groups, C_1-C_6 alkoxy, acetyl, acetamido, benzyloxy, SR_{III3} being R_{III3} as above defined, C_1-C_3 perfluoroalkyl, hydroxy, C_1-C_6 carboxyalkyl, NO_2 , amino, mono- or di-alkyl-amino C_1-C_6 ; sulphamoyl, di-alkyl sulphamoyl C_1-C_6 , or di-fluoroalkylsulphamoyl as above defined; or R_{xx1} together with R_{xx11} is a C_1-C_6 alkylen dioxy;

the compounds are preferred wherein R_{xx10} is H, the linking group is in position 2, R_{xx1} is H, R_{xx11} is

chlorine and is in para position with respect to nitrogen;

R_{3a} is H, R_{2a} is methyl and X is O;

- when R_{1a} is as defined in formula (XXXV), tiaprofenic acid residue:

Ar is phenyl, hydroxyphenyl optionally mono- or polysubstituted with halogen, alkanoyl and alkoxy C_1-C_6 , C_1-C_6 , preferably C_1C_3 , trialkyl, cyclopentyl, cyclohexyl, cycloheptyl, heteroaryl, preferably thienyl, furyl optionally containing OH, pyridyl;

the preferred compounds of (XXXV) are those wherein Ar is phenyl, R_{3a} is H, R_{2a} is methyl and X is O;

- when R_{1a} is as defined in formula (II), suprofen residue,

of which the preferred one has been indicated, wherein R_{3a} is H, R_{2a} is methyl and X = O, as described and obtained in USP 4,035,376 herein incorporated by reference;

- when R_{1a} is as defined in formula (VI), R is the residue of indoprofen when R_{2a} = H and R_{3a} = CH_3 ; of indobufen when R_{2a} is equal to H and R_{3a} = C_2H_5 ; X = O, as described and obtained according to USP 3,997,669 herein incorporated by reference;

- when R_{1a} is as defined in formula (VIII), R is the etodolac residue when R_{2a} = R_{3a} = H and X = O, as described and obtained according to USP 3,843,681 herein incorporated by reference;

- when R_{1a} is as defined in formula (VII), R is the fenoprofen residue when R_{3a} = H, R_{2a} = CH_3 and X = O, as described and obtained according to USP 3,600,437 herein incorporated by reference;

- when R_{1a} is as defined in formula (III), R is the fenbufen residue when R_{2a} = R_{3a} = H and X = O, as described and obtained according to USP 3,784,701 herein incorporated by reference;

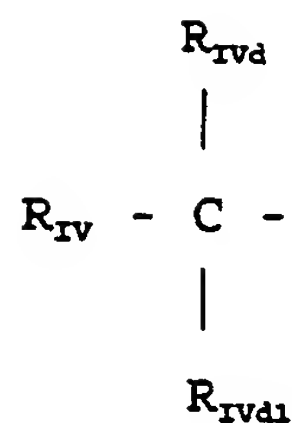
- when R_{1a} is as defined in formula (IX), R is the flurbiprofen residue when R_{3a} = H, R_{2a} = CH_3 , X = O;

- when R_{1a} is as defined in formula (X) R is the tolmetin residue when R_{2a} = R_{3a} = H, X = O, as described and obtained according to FR 1,574,570 herein incorporated by reference;

In group IIID) R_{1a} corresponds to the following formulas:

- IIIa), when $R_{2a} = H$ and $R_{3a} = CH_3$, the pranoprofen residue is obtained: α -methyl-5H-[1]benzopyran-[2,3-b]pyridin-7-acetic acid; the preferred compound has $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$;
- (XXX), when $R_{2a} = H$ and $R_{3a} = CH_3$, the bermoprofen residue is obtained: dibenz[b,f]oxepin-2-acetic acid; the preferred compound has $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$.
- (XXXI), when $R_{2a} = H$ and $R_{3a} = CH_3$, R is the radical of the compound CS-670: 2-[4-(2-oxo-1-cyclohexyliden methyl) phenyl]propionic acid; the preferred compound has $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$;
- (XXXII), when $R_{2a} = R_{3a} = H$, the Pemedolac residue is obtained; the preferred compound has $R_{2a} = R_{3a} = H$, $u = 1$ and $X = O$;
- (XXXIII), when $R_{2a} = R_{3a} = H$, the pirazolac residue is obtained: 4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolic acid derivatives;
The preferred compounds have $R_{2a} = R_{3a} = H$, $u = 1$ and $X = O$;
- (XXXVI), when $R_{2a} = H$, $R_{3a} = CH_3$, the zaltoprofen residue is obtained; when the residue is saturated with a hydroxyl or amino group, or with the carboxylic function the compounds are known as dibenzothiepine derivatives; the preferred compounds have $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$;
- (XXXVII), when $R_{2a} = R_{3a} = H$ the mofezolac residue is obtained: 3,4-di(p-methoxyphenyl)isoxazol-5-acetic acid when the residue is CH_2-COOH ; the preferred compounds have $R_{2a} = R_{3a} = H$, $t = 1$ and $X = O$;
- (XII), when $R_{2a} = R_{3a} = H$ the bromfenac residue is obtained: 2-amino-3-(4-bromobenzoyl)benzeneacetic acid; the preferred compounds have $u = 1$, $t = 1$, $X = O$, $R_{2a} = R_{3a} = H$; or $t = 0$;

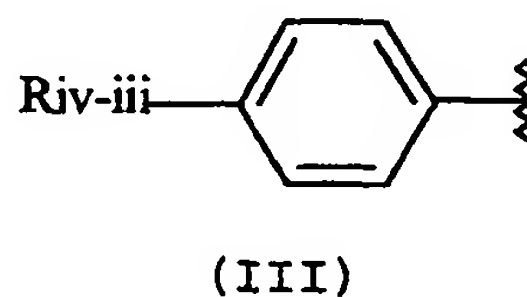
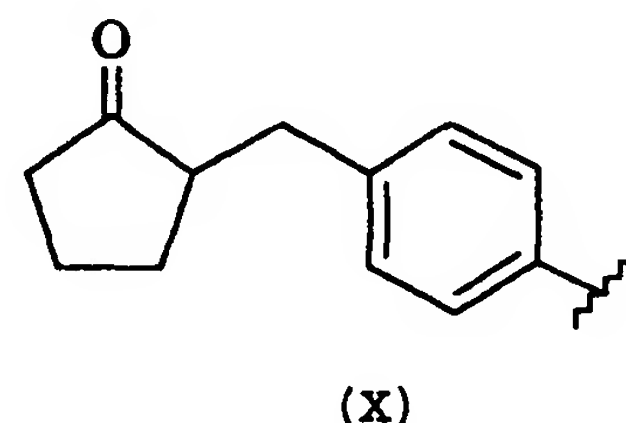
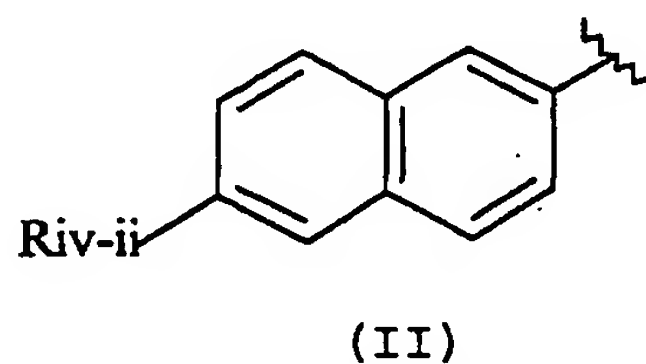
in group IV) wherein $t = 1$, $u = 1$, R is



wherein:

R_{IVd} and R_{IVd1} are at least one H and the other a linear or branched when possible $C_1 - C_6$, preferably C_1 and C_2 alkyl, or difluoroalkyl with the alkyl from 1 to 6 carbon atoms, C_1 is preferred, or R_{IVd} and R_{IVd1} form together a methylene group;

R_{IV} has the following meaning:



wherein the compounds of group IV) have the following meanings:

- in formula (II)

R_{IV-ii} is $C_1 - C_6$ alkyl, $C_3 - C_7$ cycloalkyl, $C_1 - C_7$ alkoxyethyl, $C_1 - C_3$ trifluoroalkyl, vinyl, ethynyl, halogen, $C_1 - C_6$ alkoxy, difluoroalkoxy, with $C_1 - C_7$ alkyl, $C_1 - C_7$ alkoxy-methoxy, alkylthiomethoxy with $C_1 - C_7$ alkyl, alkyl methylthio with $C_1 - C_7$ alkyl, cyan, difluoromethylthio, phenyl- or phenylalkyl substituted with $C_1 - C_6$ alkyl; preferably R_{IV-ii} is CH_3O- , R_{IVd} is H and R_{IVd1} is CH_3 , and it is known as naproxen residue;

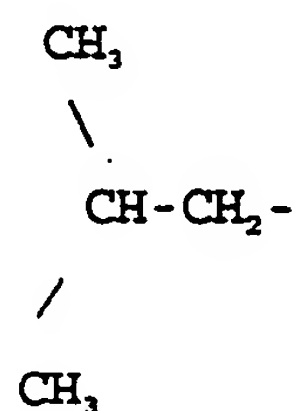
$X = O$ and X_1 is as above defined for Ia);

- in formula (X), of which the loxoprofen residue, described in USP 4,161,538 herein incorporated by reference, has been indicated, the compounds wherein R_{IVd}

is H and R_{IVd1} is CH_3 , $X = O$ and X_1 is as above defined for Ia) are preferred;

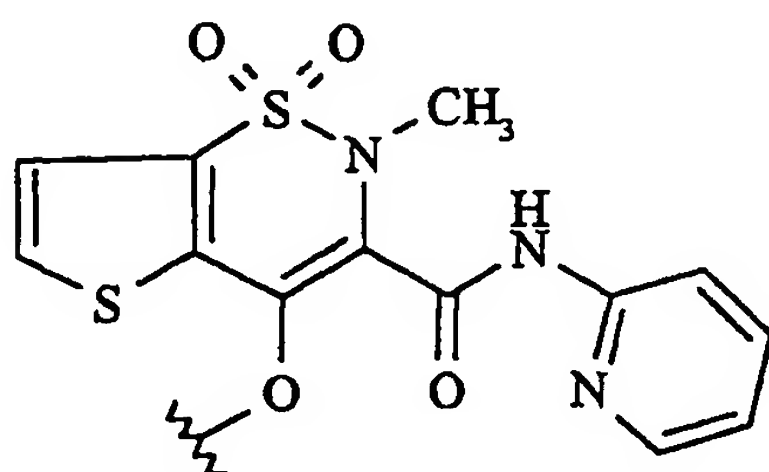
- in formula (III):

R_{IV-III} is a C_2-C_5 alkyl, optionally branched when possible, C_2 and C_3 alkyloxy, allyloxy, phenoxy, phenylthio, cycloalkyl from 5 to 7 carbon atoms, optionally substituted in position 1 by a C_1-C_2 alkyl; it is preferred the compound wherein R_{IV-III} is

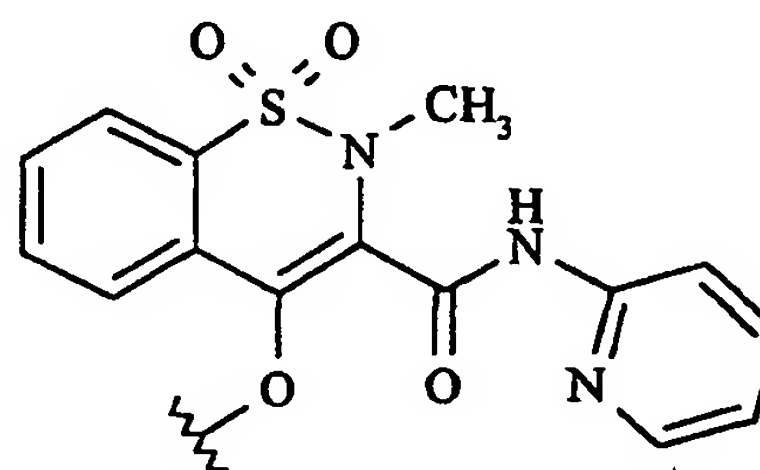


and $R_{IVd} = H$, R_{IVd1} is CH_3 , compound known as ibuprofen residue; $X = O$ and X_1 is as above defined for Ia);

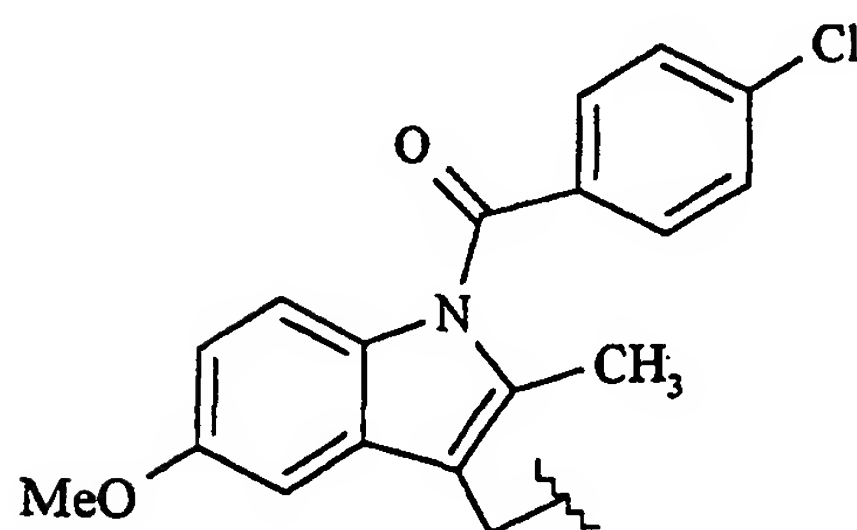
Group V)



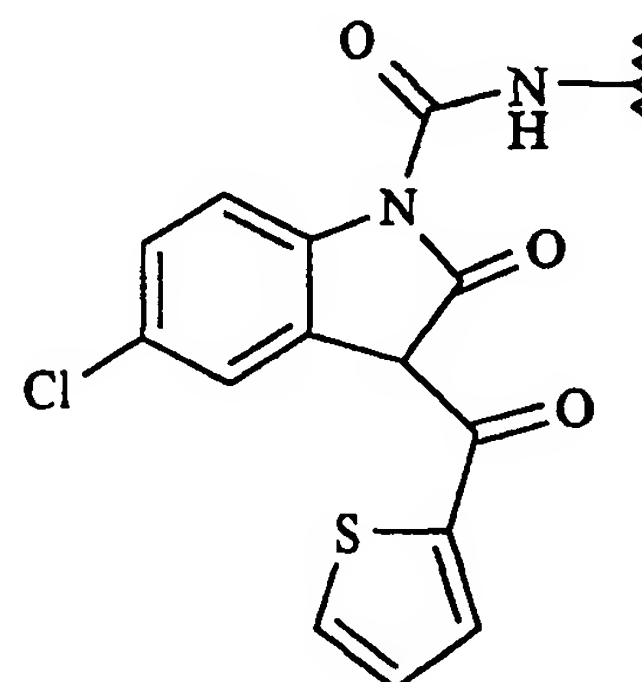
(VII)



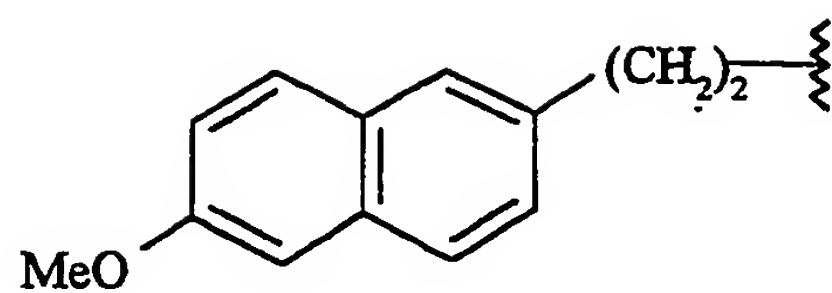
(IX)



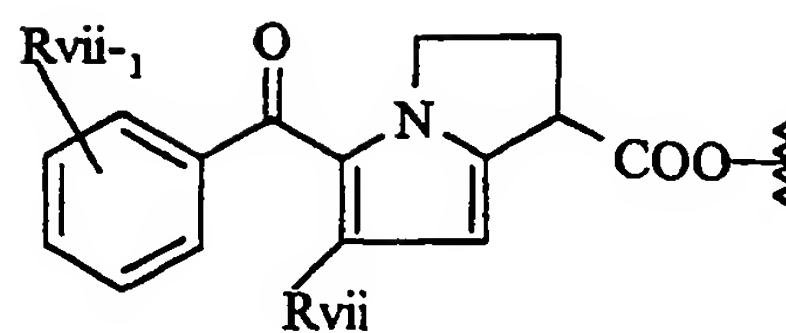
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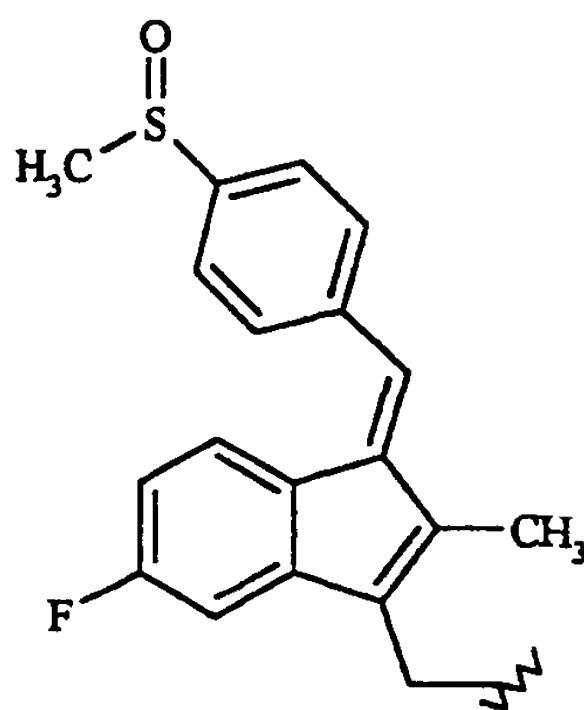
(V)



(III)

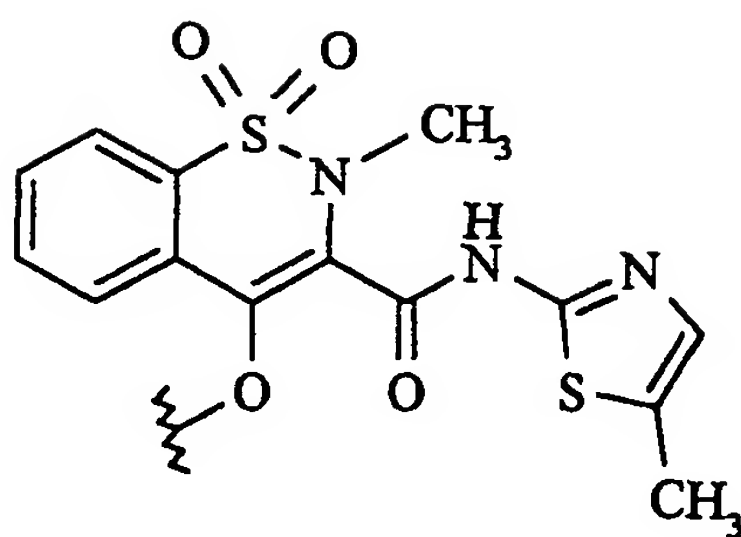


(II)

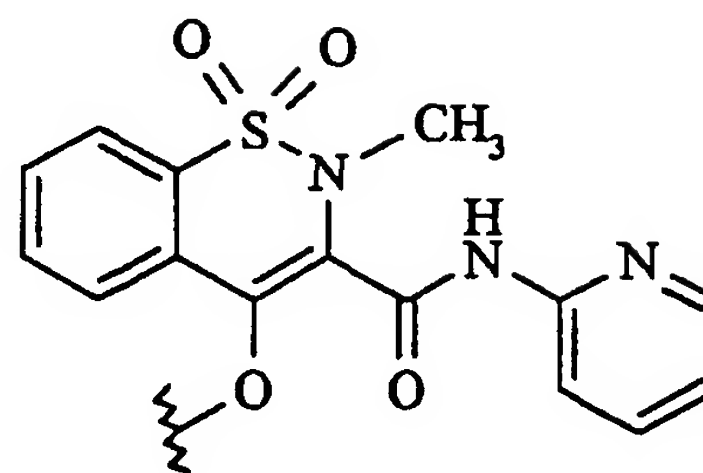


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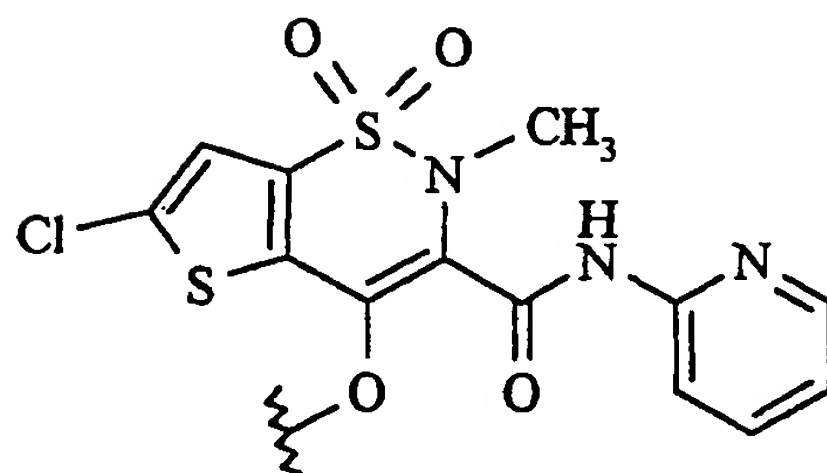
Group VE)



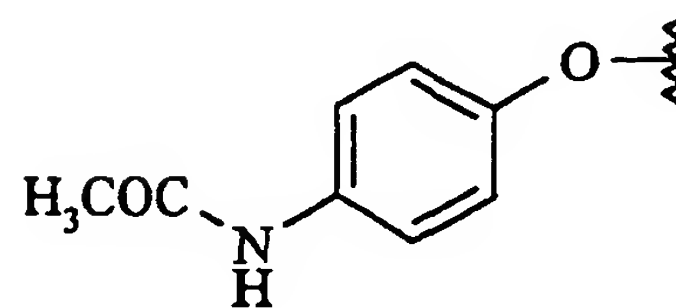
(X)



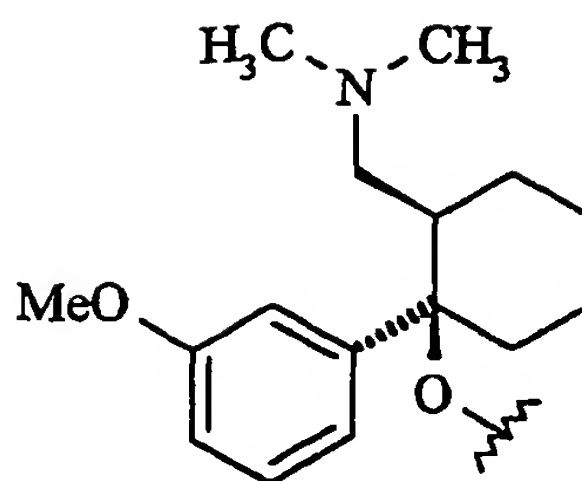
(XI)



(XIII)



(XXXX)



(XXXXI)

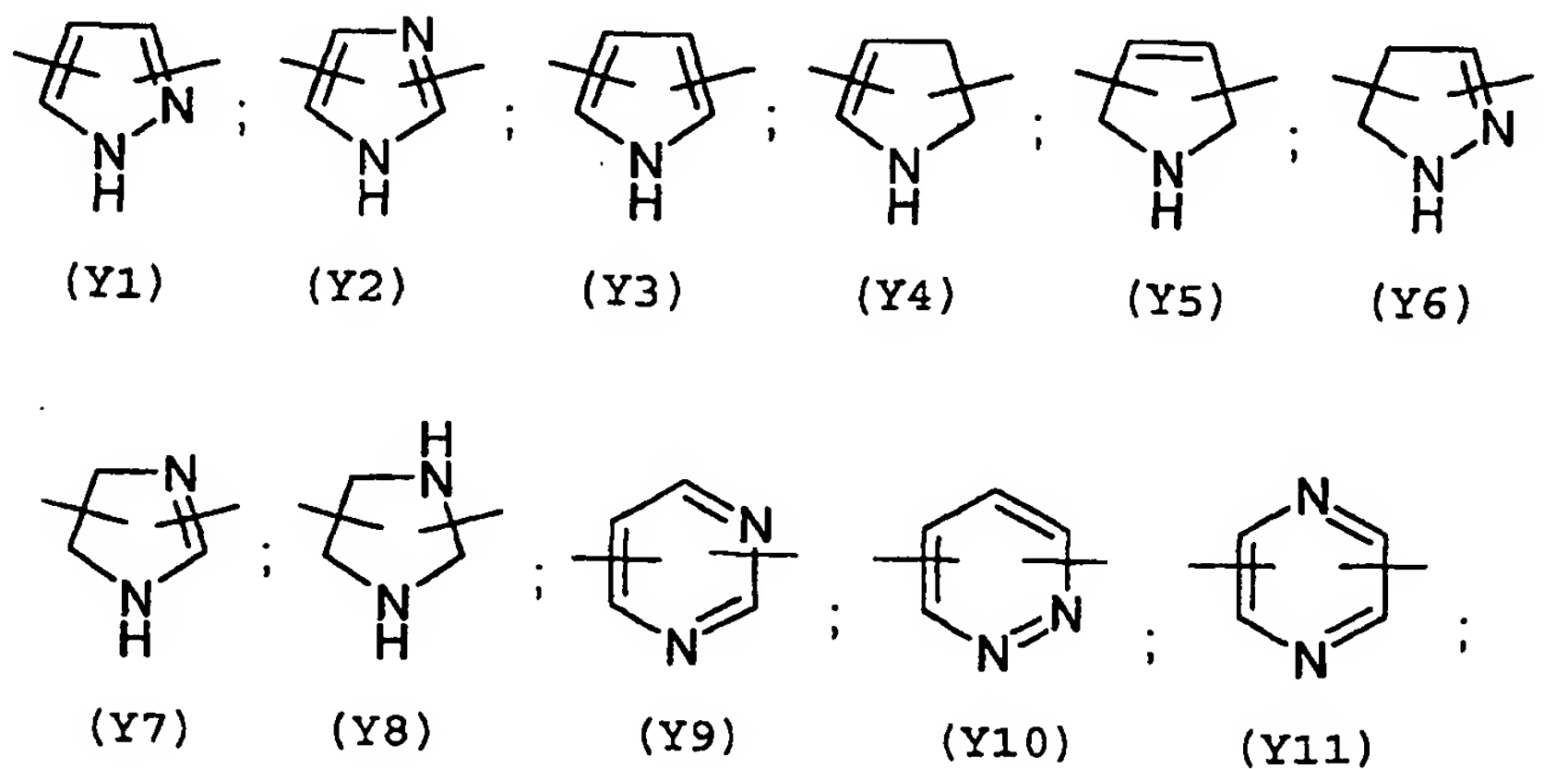
in group V), the compounds have the following meanings:

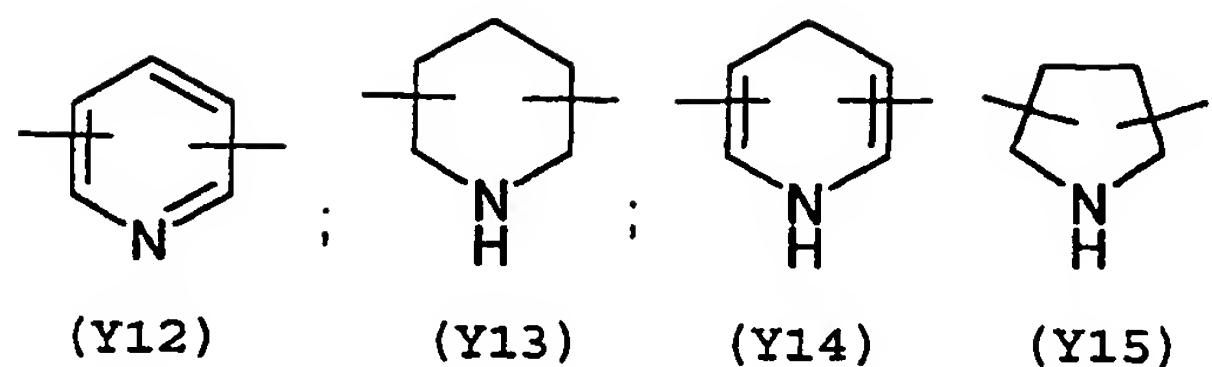
- when R is formula (II),
 R_{VII} is H or a linear or branched when possible C₁-C₄ alkyl;
 R_{VII-1} is R_{VII} , or a linear or branched when possible C₁-C₄ alkoxy; Cl, F, Br; the position of R_{VII-1} being ortho, or metha, or para;
 the residue of the known Ketorolac is preferred, wherein R_{VII} and R_{VII-1} are H, and A = R (A being the group of the formula A-X₁-NO₂) and t = 0;
- when R is formula (V),
 of which the residue of the known tenidap has been indicated, as described and obtained in USP 4,556,672 herein incorporated by reference;
 in these compounds of formula (V) A = R and t = 0,
- when R is formula (VII),
 of which the residue of the known tenoxicam has been indicated, A is RCO, t = 1 u = 0 or A is R and t = 0, as described and obtained in DE 2,537,070 herein incorporated by reference;
- when R is formula (IX),
 wherein A = R and t = 0, or A = RCO with t = 1 and u = 0, the residue of the known piroxicam has been indicated, as described and obtained in USP 3,591,584 herein incorporated by reference;
- when R is formula (III)
 wherein A = RCOO, t = 1 and u = 0 or 1; or t = 0 and A = R, of which the residue of the known nabumetone has been indicated, as described and obtained in USP 4,061,779 herein incorporated by reference;
- when R is formula (IV)
 wherein A = RCOO, t = 1 and u = 1,

of which the indomethacin residue has been indicated, as described and obtained in USP 3,161,654, herein incorporated by reference;

- when R = formula (LX) and in $(COX_u)_t$, $u = t = 1$ and X is oxygen, the precursor compound is known as sulindac;
 - when R is formula (X), the X residue is known as meloxicam; the preferred compounds are those wherein $A = RCO$, $t = 1$ and $u = 0$;
 - when R is formula (XI) the residue is known as ampiroxicam when the termination is $-CH(CH_3)OCOC_2H_5$; the preferred compounds have $A = RCO$, $t = 1$ and $u = 0$;
 - when R is formula (XIII) and the valence is saturated with H, the residue derives from lornoxicam; the preferred compounds have $A = RCO$, $t = 1$ and $u = 0$;
 - when R is formula (XXXX) and the valence is saturated with H the compound known as paracetamol is obtained, as described and obtained in USP 2,998,450 herein incorporated by reference;
 - when R is formula (XXXXI) and the valence is saturated with H, the compound known as Tramadol is obtained, as described and obtained in USP 3,652,589;
- the preferred compounds according to the present invention obtainable with the radicals corresponding to the formulas (XXXX) and (XXXXI) have $A = RCO$, $t = 1$ and $u = 0$.

Preferably Y is selected from the following:





Preferably Y is an aromatic ring having 6 atoms, containing one nitrogen atom, said aromatic ring having the two free valences in position 2 and 6.

The preferred of Y is Y12 (pyridyl) substituted in position 2 and 6. The bonds can be also in a non symmetric position, for example Y12 (pyridyl) can be substituted also in position 2 and 3; Y1 (pyrazol) can be 3,5-disubstituted.

The X₁ precursors as defined by formula (B), wherein the free valence of the oxygen is saturated with H and the free valence of the end carbon is saturated with either a carboxylic or hydroxyl group, are commercially available compounds or they can be obtained by known methods of the prior art.

The compounds containing R of group I of the type Ia) are described in patent application WO 92/01668 wherein also the preparation methods are mentioned. This patent is herein incorporated by reference. The compounds of type Ib) are for example prepared by using the method indicated in The Merck Index, XI ed., 1989, pag. 16, No. 95 for the acetylsalicylsalicylic acid residue. The modifications of the compounds of formula Ib) can be obtained by using the processes mentioned in patent application WO 92/01668.

The compounds wherein R is of group II) are described in patent application WO 94/04484 and USP 3,558,690 wherein also the preparation methods are indicated. These patents are herein incorporated by reference.

The starting compound of IIb), when the valence is saturated with -COOH (flunixin), is obtained according to USP 3,337,570 and USP 3,689,653, both herein incorporated by reference. The compounds containing the substituents mentioned in the previous patents are equivalent to flunixin.

The compounds wherein R is of group III) are described and obtained by the processes mentioned in the following patents:

patent application PCT/EP/93 03193; for the compounds of formula (IV) see also USP 3,641,127; for the compounds of formula (XXI) see also USP 3,896,145; for the compounds of formula (IX) flurbiprofen residue see also USP 3,755,427; for the compounds of formula (II) see also USP 4,035,376; for the compounds of formula (VI) see also USP 3,997,669; for the compounds of formula (VIII) see also USP 3,843,681; for the compound of formula (VII) see also USP 3,600,437; for the compounds of formula (III) see also USP 3,784,701. All these mentioned patents are herein incorporated by reference.

The procedures for the preparation of the compounds of class IIID) are the following:

The residue IIIa) is obtained by preparing the acid compound according to USP 3,931,205, the valence is saturated with $-\text{CH}(\text{CH}_3)-\text{COOH}$. The compounds containing the substituents mentioned in the previous patent are equivalent to pranoprofen. The residue (XXX) is prepared through the compound with the group $-\text{CH}(\text{CH}_3)-\text{COOH}$ (bermoprofen) according to USP 4,238,620 herein incorporated by reference. Other equivalent products are described in the above mentioned patent.

The residue (XXXI) is prepared by starting from the corresponding acid $-\text{CH}(\text{CH}_3)-\text{COOH}$ according to USP 4,254,274. Equivalent compounds are described in the same patent.

The residue (XXXII) is prepared according to EP 238,226 herein incorporated by reference, when the valence is saturated with $-\text{CH}_2-\text{COOH}$. Equivalent products are reported in said patents as 1,3,4,9 tetrahydropyran [3,4-b] indol-1-acetic substituted acids.

The residue (XXXIII) is prepared from pirazolac and the valence is saturated with $-\text{CH}_2-\text{COOH}$, as indicated in EP 54,812 herein incorporated by reference. Equivalent products are described in said patent.

The residue (XXXVI) is prepared according to UK 2,035,311 herein incorporated by reference, by starting from zaltoprofen and having the $-\text{CH}(\text{CH}_3)-\text{COOH}$ termination. Equivalent products are described in said patent.

The process for preparing the residue (XXXVII) is obtained starting from mofezolac and it is prepared according to EP 26,928. Equivalent products are reported in the same patent.

The compounds wherein R is of group IV) are described in GB patent application 2,283,238, wherein also the preparation methods are indicated; this patent is herein incorporated by reference.

In group IV) the compounds can also be obtained: for the compounds of formula (II) using USP 3,904,682; the compounds of formula (X) according to USP 4,161,538; the compounds of formula (III) according to USP 3,228,831. The herein mentioned patents are incorporated in the present application by reference.

In group V) the compounds can also be obtained: for the compounds of formula (II) using USP 4,089,969 herein incorporated by reference; the compounds of formula (V) can be obtained according to USP 4,556,672 herein incorporated by reference.

The residue (X) is prepared according to the German patent 2,756,113. Equivalent products are described in said patent.

The residue (XI) is prepared according to EP 147,177, herein incorporated by reference, starting from ampiroxicam having the termination $-\text{CH}(\text{CH}_3)\text{OCOOC}_2\text{H}_5$. Equivalent products are described in said patent.

The residue (XII) is prepared according to J. Med. Chem., vol. 27 No. 11, Nov. 1984, Walsh et Al. "Antiinflammatory Agents. 3. Synthesis and Pharmacological Evaluation of 2-amino-3-benzoylphenylacetic Acid and Analogues", herein incorporated by reference. Equivalent products are described in said publication.

The residue (XIII) is prepared starting from lornoxicam, wherein the valence is saturated with H. It is prepared according to GB 2,003,877. Equivalent products are described in said patent.

The residue (LX) in group V is prepared from Sulindac, obtained according to US 3,654,349.

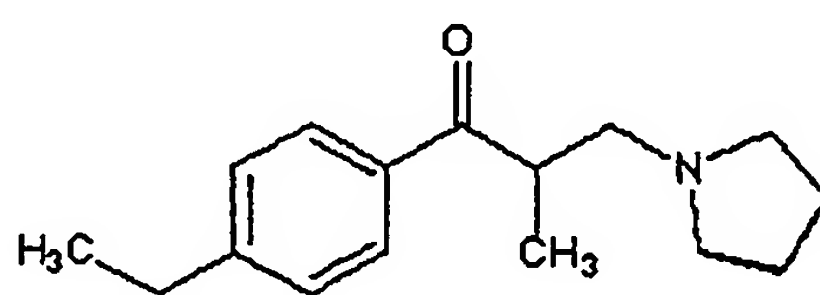
In general the connection between A and X_1 is, as seen, of ester or amidic type (NH or NR_{1c} , as defined in X) when R is of groups I, II, III, IV and V. For the formation of such connection all the synthesis routes well known for the formation of such bonds are usable.

The preparation of the compounds of formula $\text{A-X}_1\text{-N(O)}_z$ with the linking group X_1 of formula (B) is described in

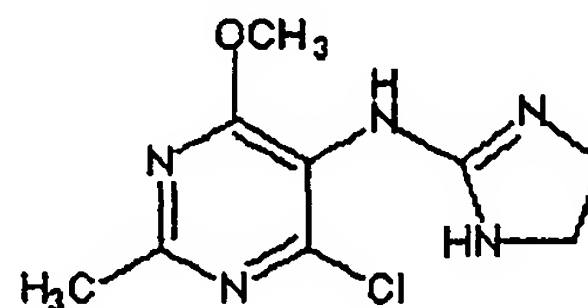
published PCT application WO 00/51988 in the name of the Applicant, herein incorporated by reference.

The compounds of group A), as said, are effective in the incontinence treatment, they give lower side effects and are also parenterally administrable, therefore overcoming the drawbacks of the prior art mentioned in patent application WO 98/09948.

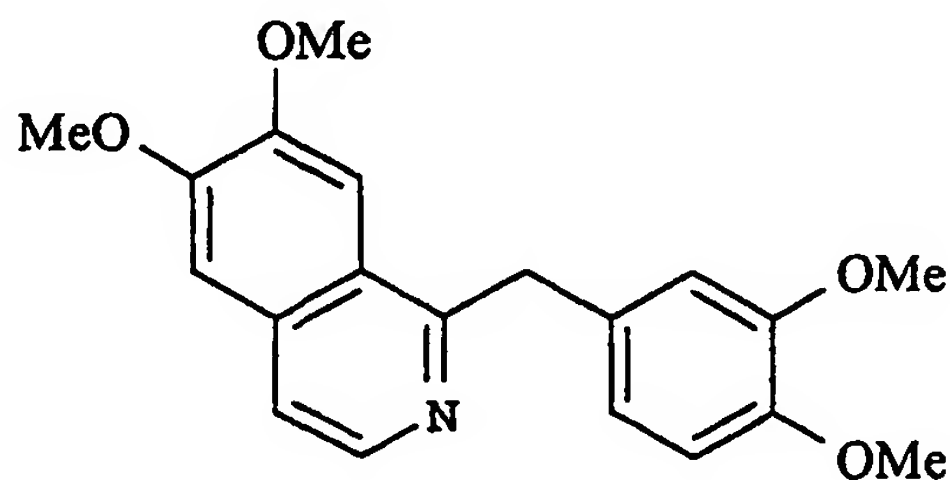
The drugs of the nitrate salts compounds B') are selected from B'1) anticholinergic drugs, B'2) calcium-antagonist drugs, B'3) drugs which facilitate the opening of the potassium channels, B'4) alpha-adrenergic agonistic drugs, B'5) alpha-adrenergic antagonist drugs, B'6) beta-adrenergic agonist drugs, B'7) antidepressant drugs, B'8) GABA agonist drugs, B'9) agonist drugs of the muscarinic receptor, and B'10) other drugs selected from inaperizone (B'10b), moxonidine (B'10c), papaverine (B'10e), benzydamine (B'10g):



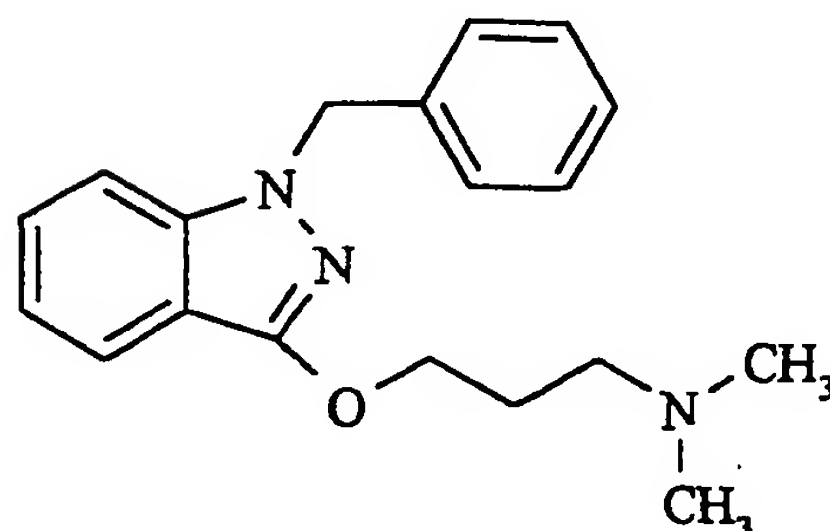
(B'10b)



(B'10c)



(B'10e)

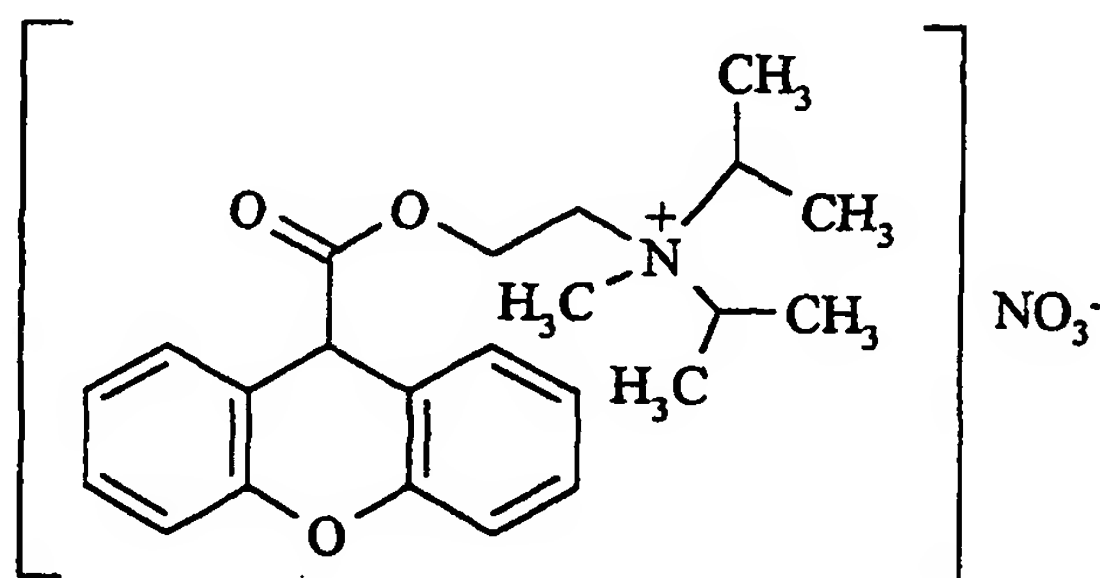


(B'10g)

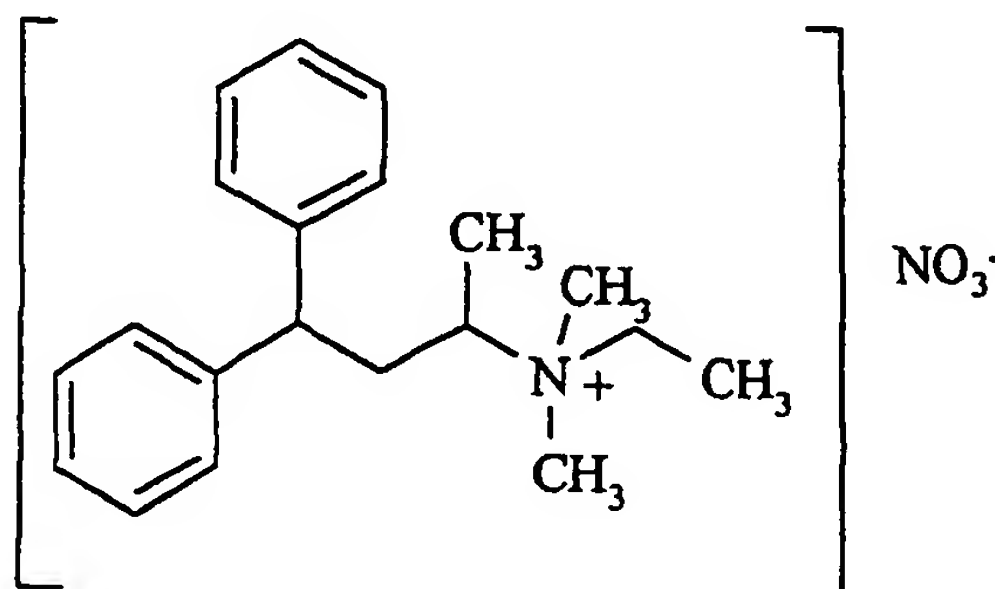
B11) serotoninergetic antagonist drugs of the 5-HT₄ receptor.

In particular, compounds B') are selected from the following:

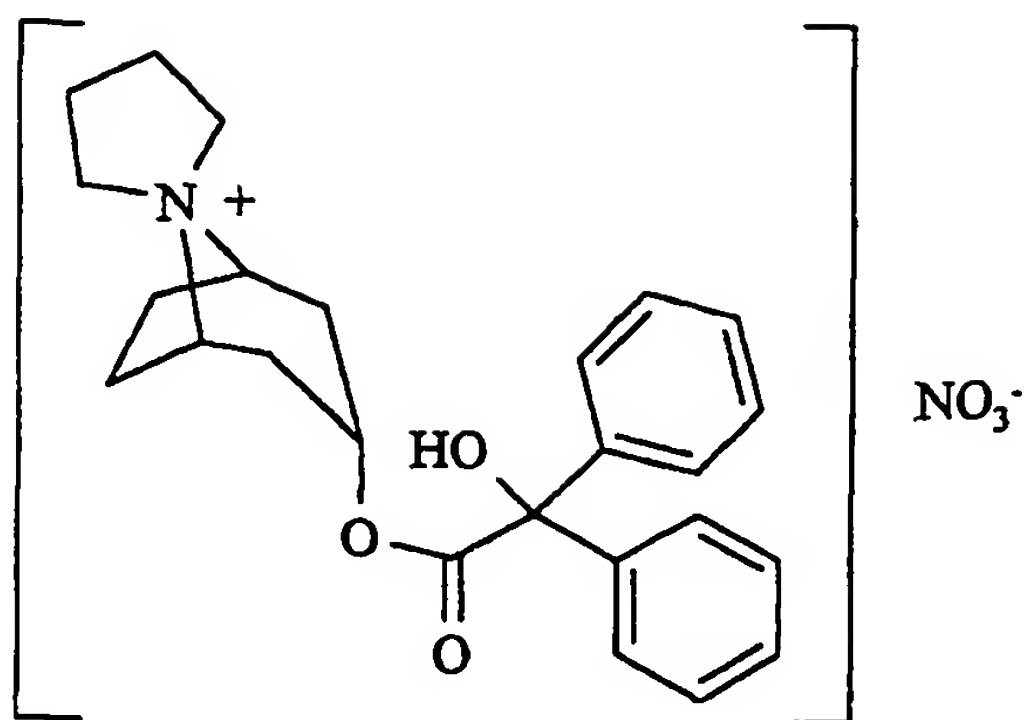
- B'1) propantheline (B'1a), emepronium (B'1b), trospium (B'1c), tolterodine (B'1d), darifenacin (B'1e), vamicamide (B'1f), zamifenacin (B'1g), atropine (B'1h), cycloidine (B'1i), oxybutynin (B'1j), N-desethyl-oxybutynin (B'1j-I), dicyclomine (B'1m), propiverine (B'1n), flavoxate (B'1o), terodiline (B'1p);
- B'2) nifedipine (B'2a), flunarizine (B'2b), diltiazem (B'2c);
- B'3) pinacidil;
- B'4) ephedrine (B'4a), pseudoephedrine, phenylpropanolamine (B'4c), midodrine (B'4d), de-glymidodrine (B'4e);
- B'5) alfuzosin (B'5a), doxazosin (B'5b), prazosin (B'5c);
- B'6) clenbuterol (B'6a), terbutaline (B'6b), formoterol (B'6c);
- B'7) imipramine (B'7a), clozapine (B'7b), milnacipran (B'7c), fluphenazine (B'7d), nortriptyline (B'7e), duloxetine (B'7f);
- B'8) baclofen;
- B'9) bethanechol;



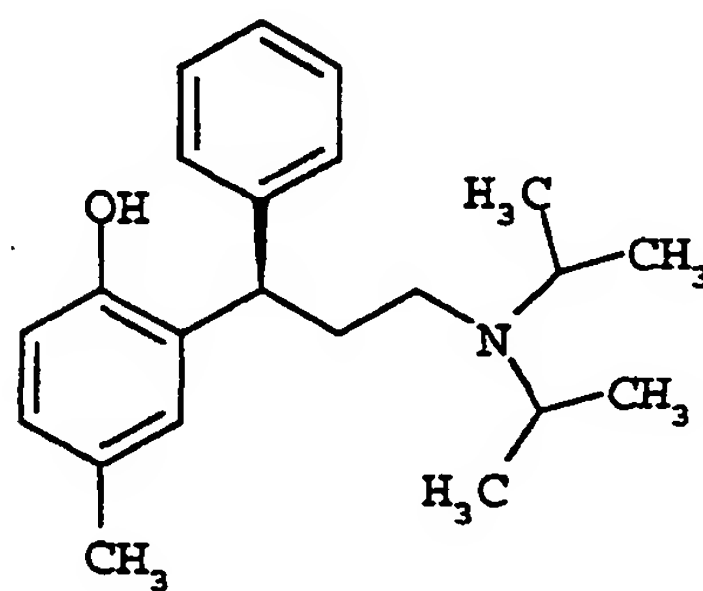
(B'1a)



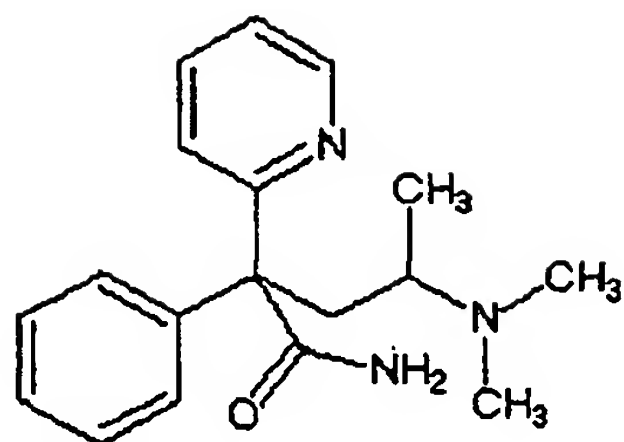
(B'1b)



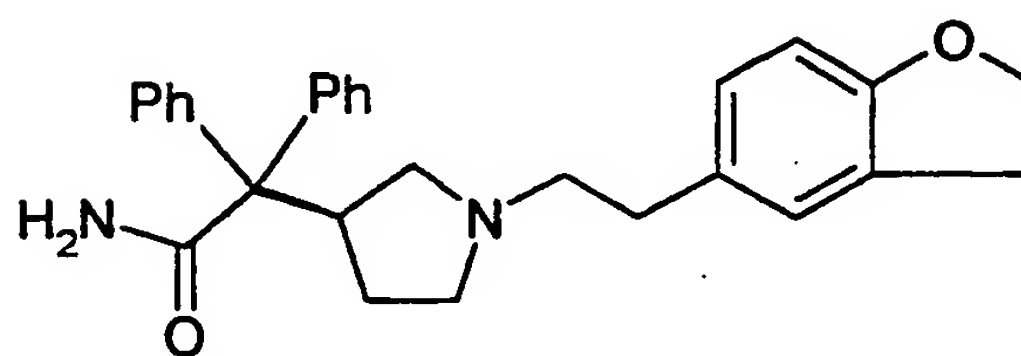
(B'1c)



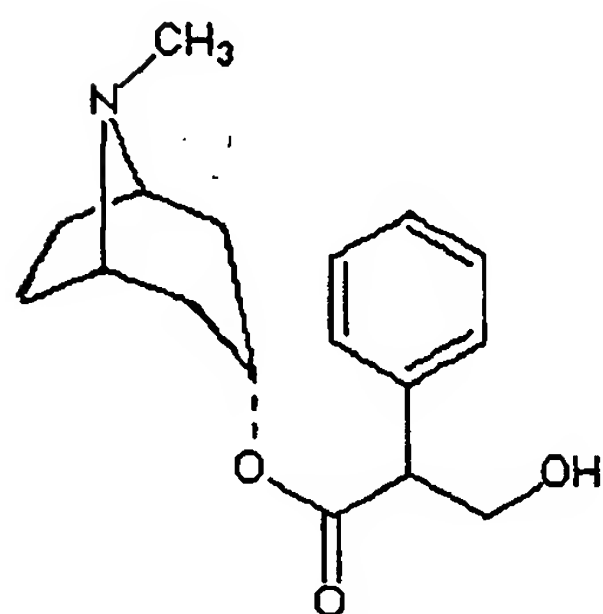
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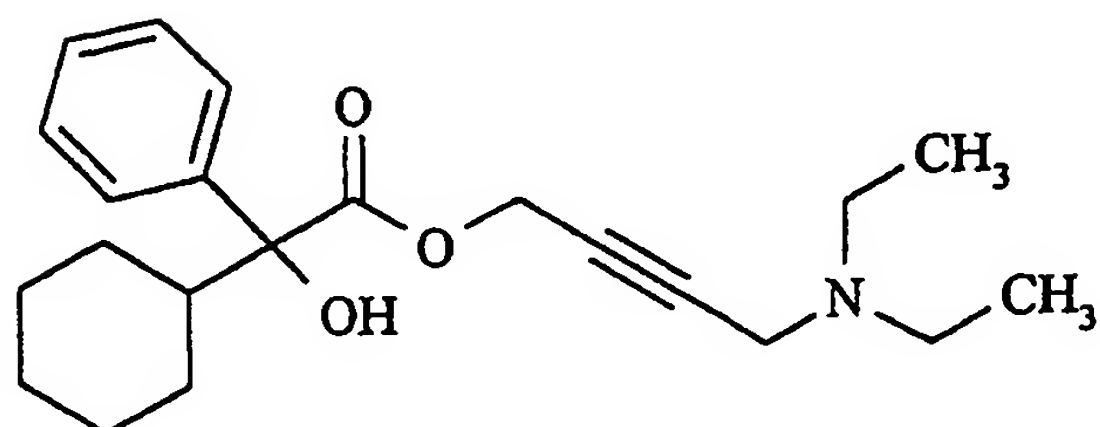
(B'1f)



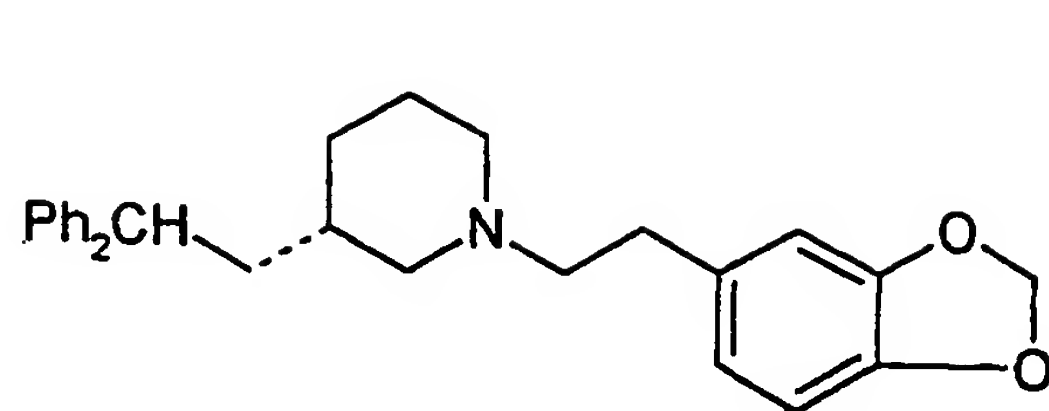
(B'1e)



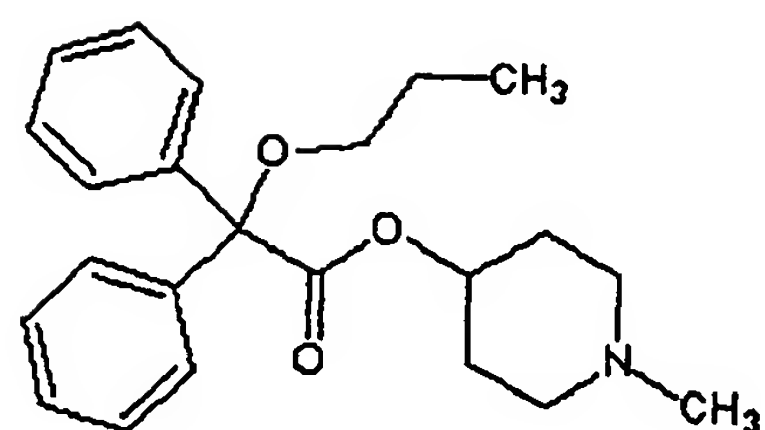
(B'1h)



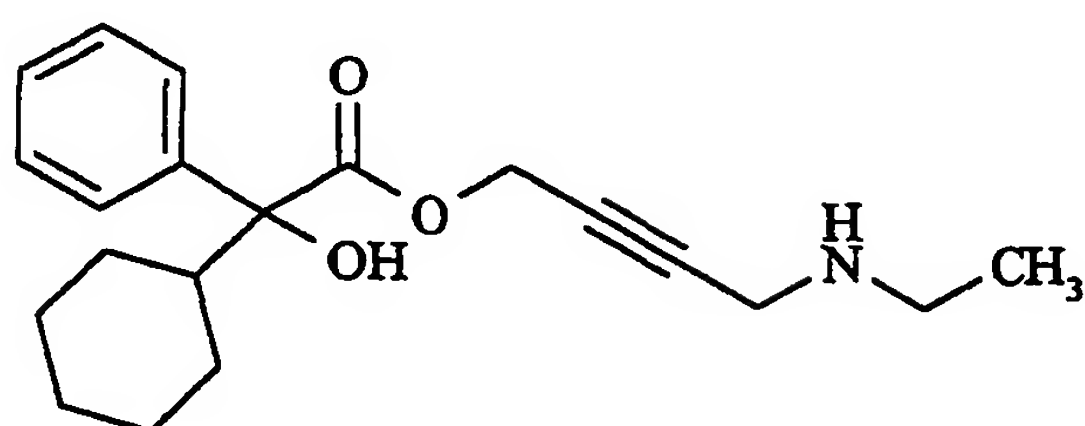
(B'1l)



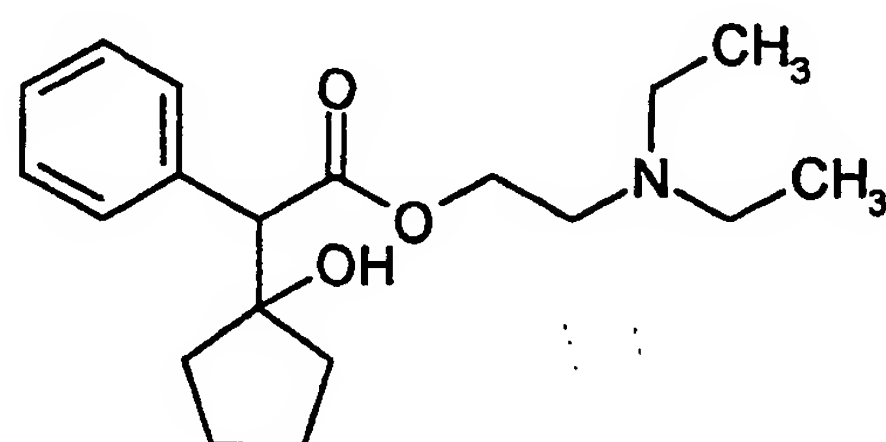
(B'1g)



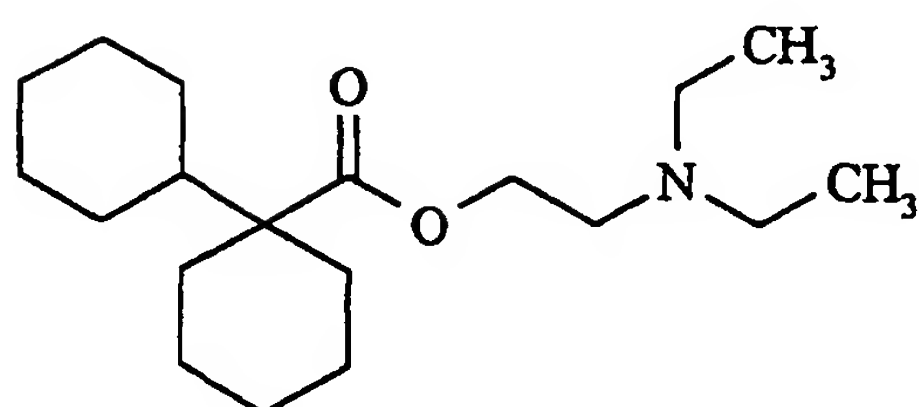
(B'1n)



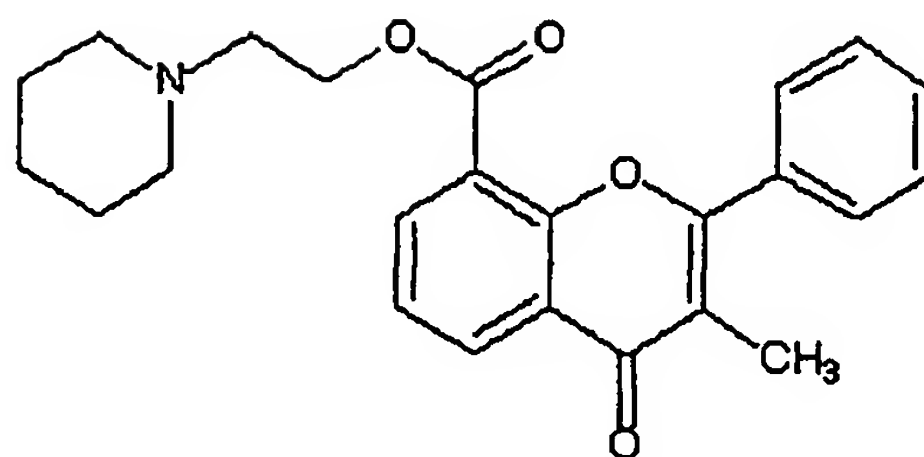
(B'11-I)



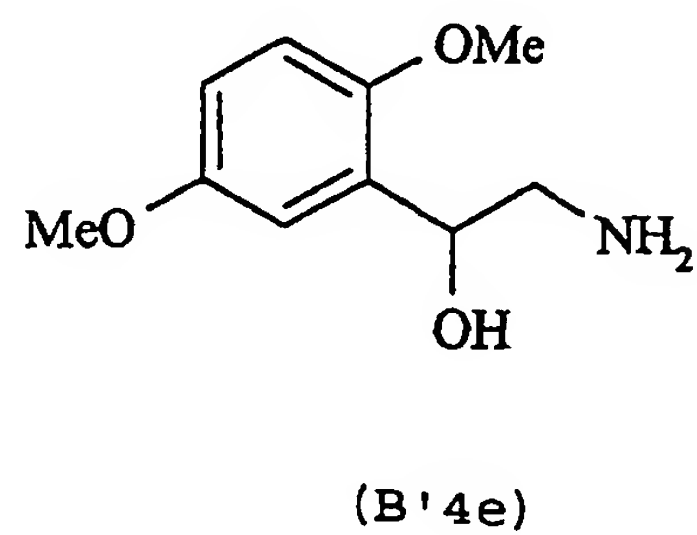
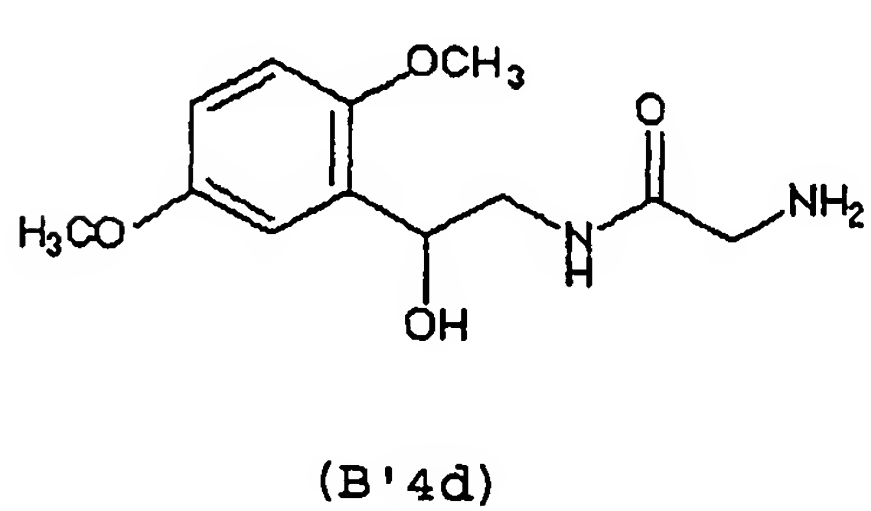
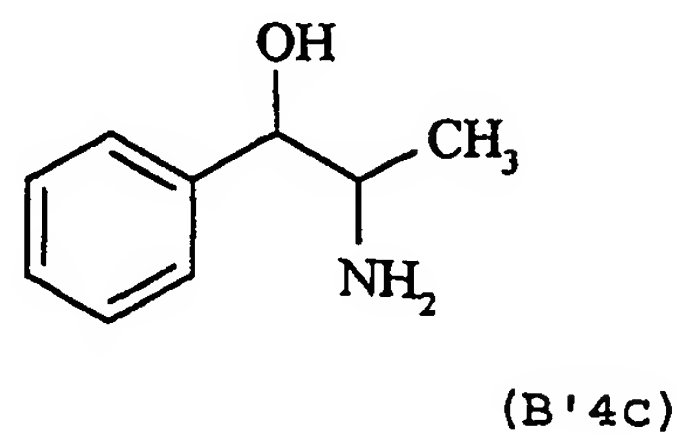
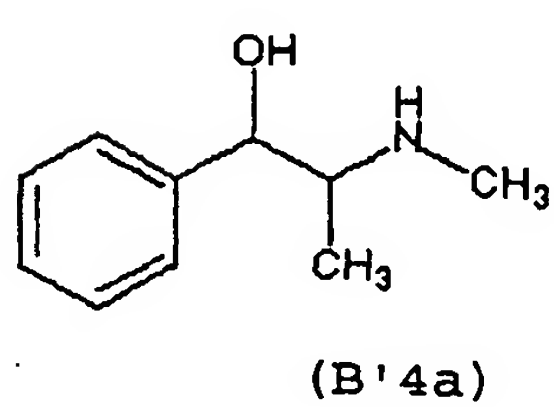
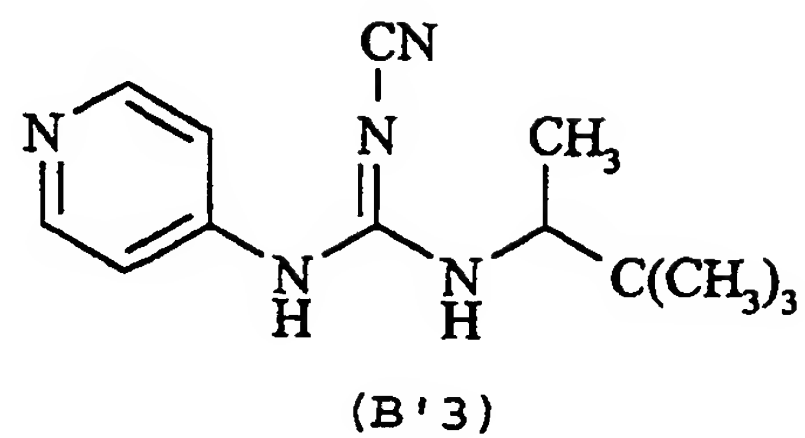
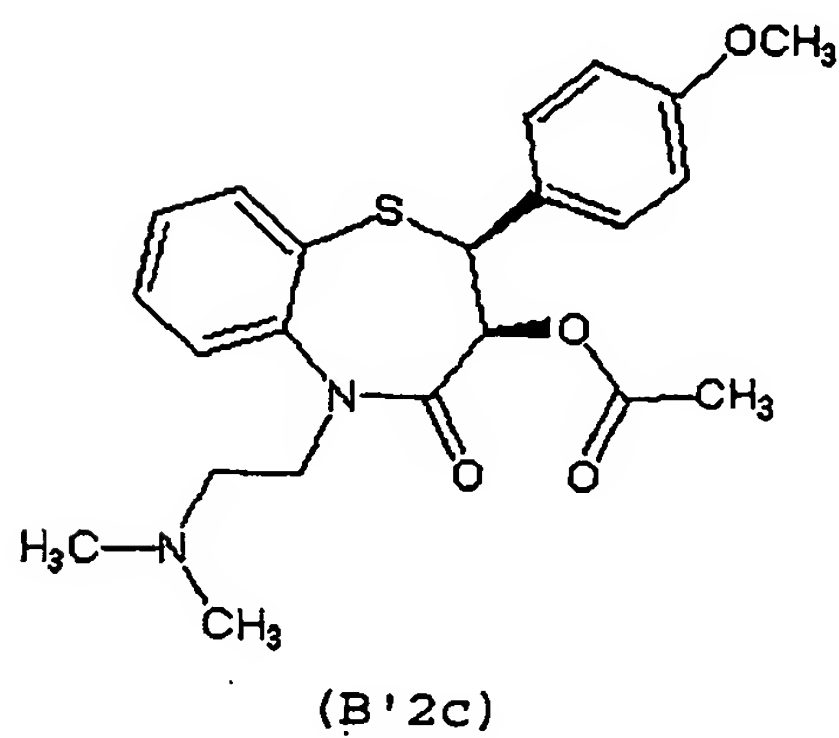
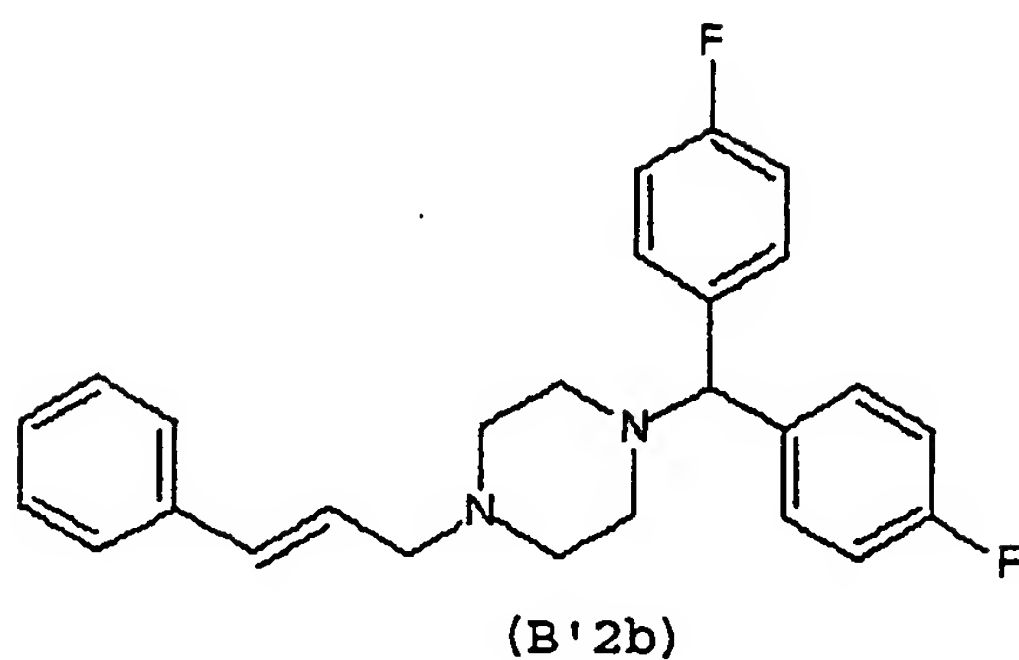
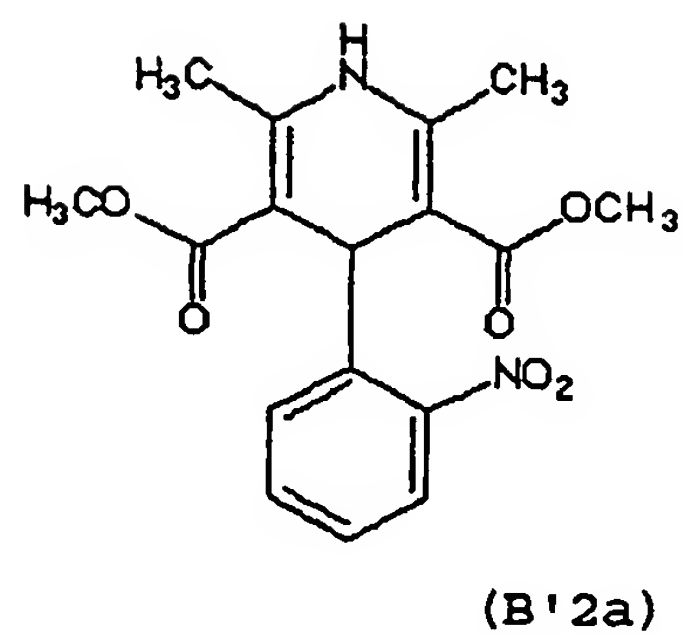
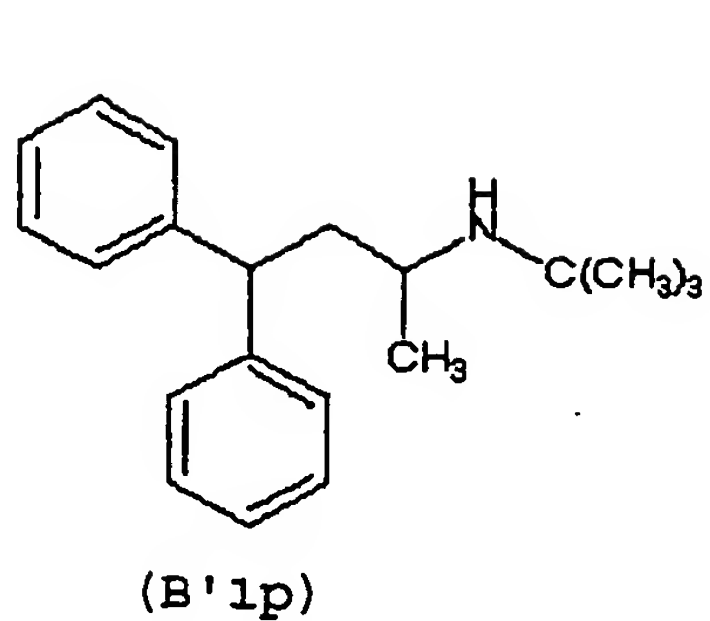
(B'11i)

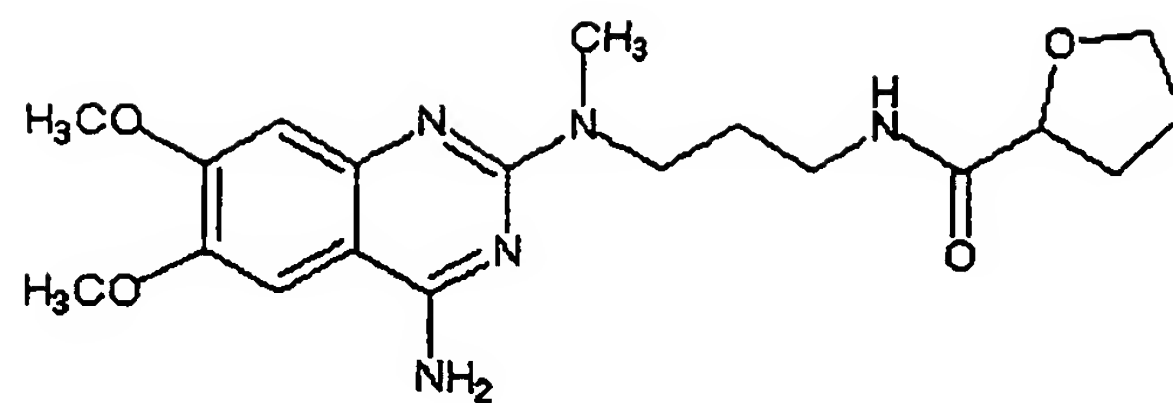


(B'1m)

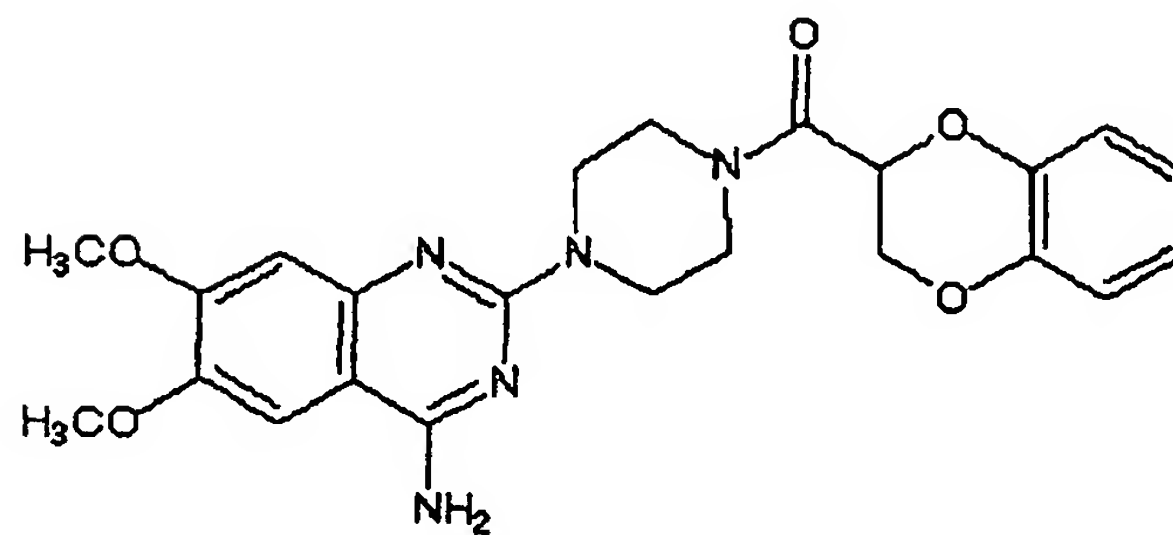


(B'1o)

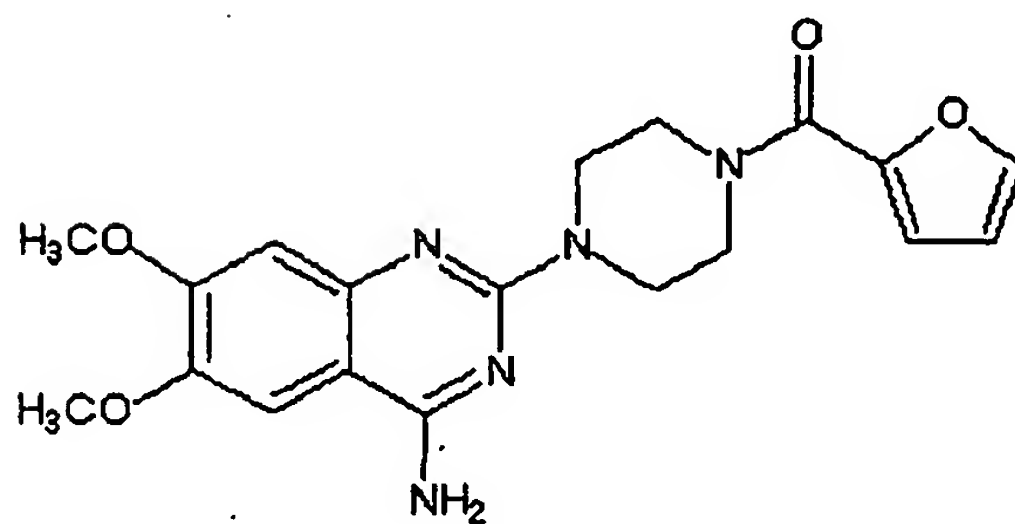




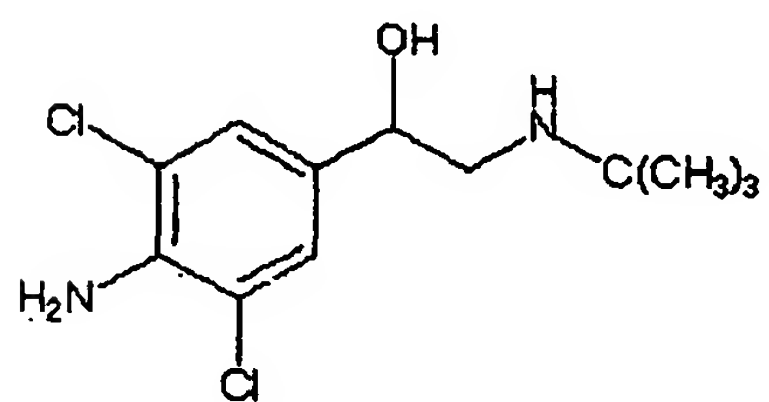
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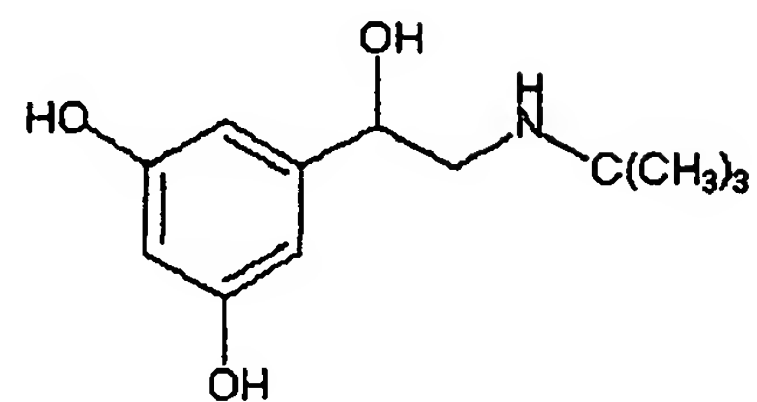
(B' 5b)



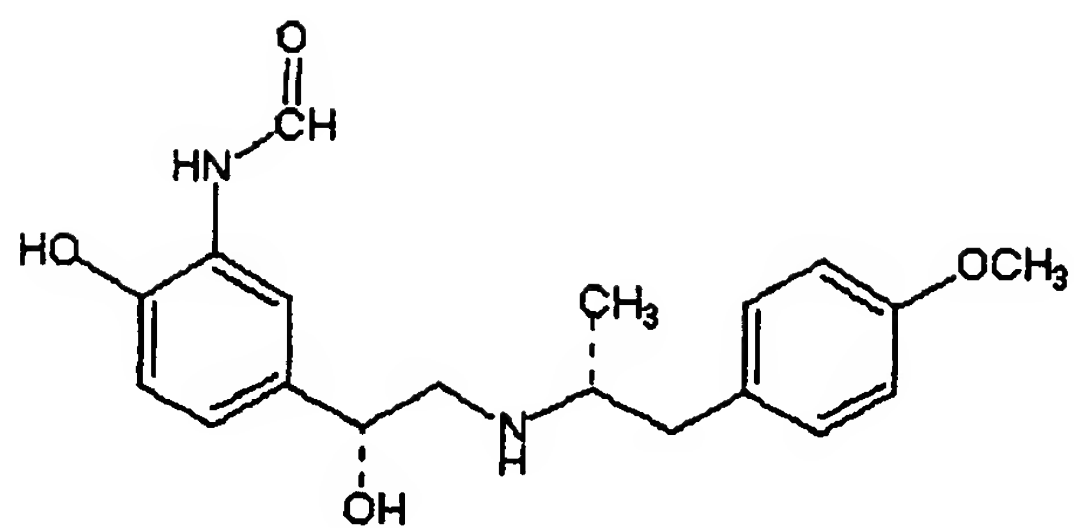
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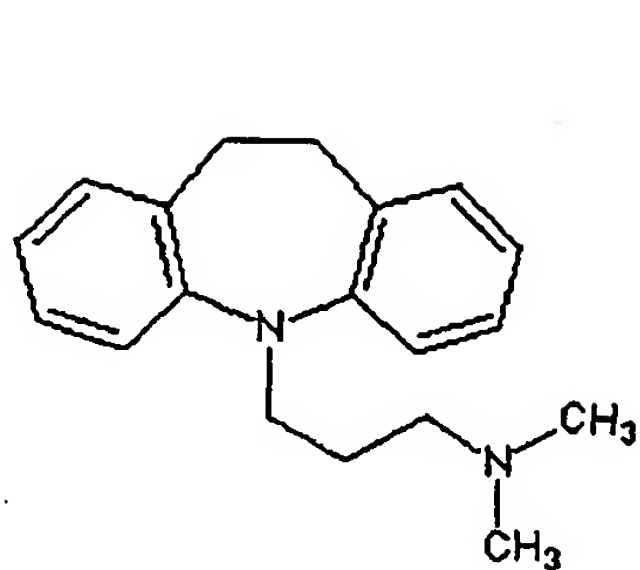
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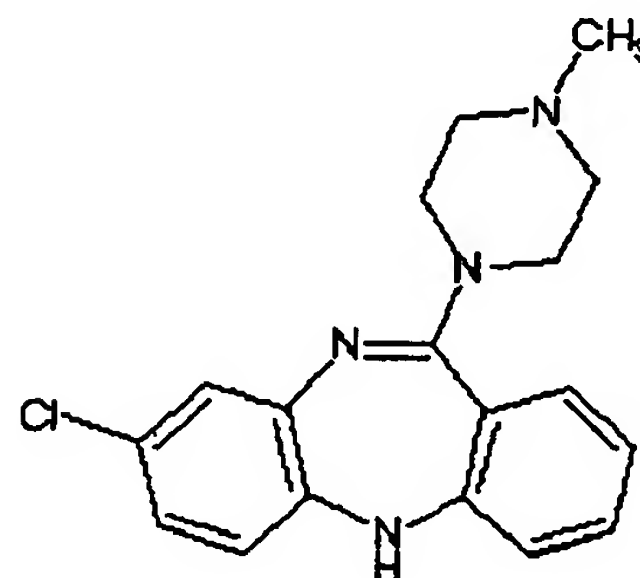
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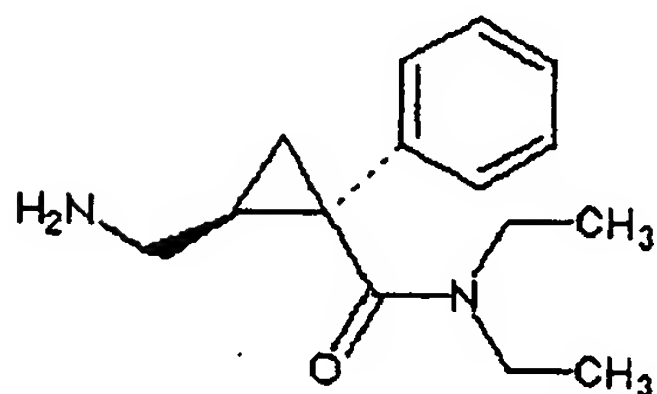
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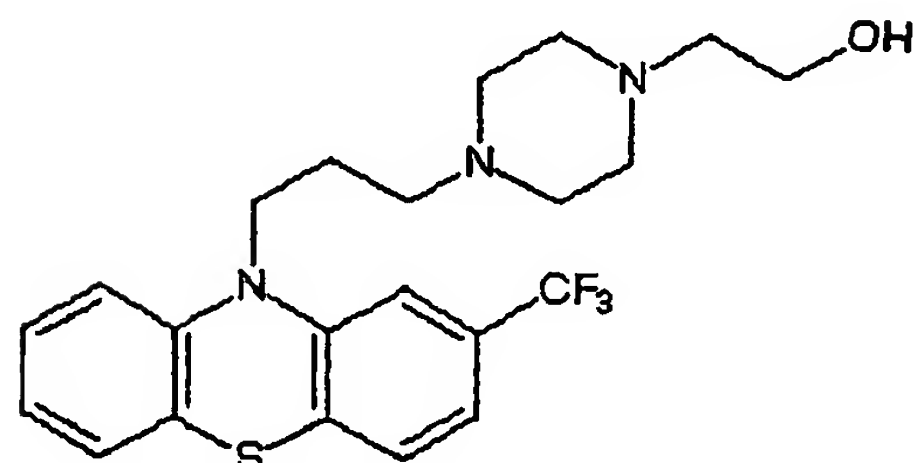
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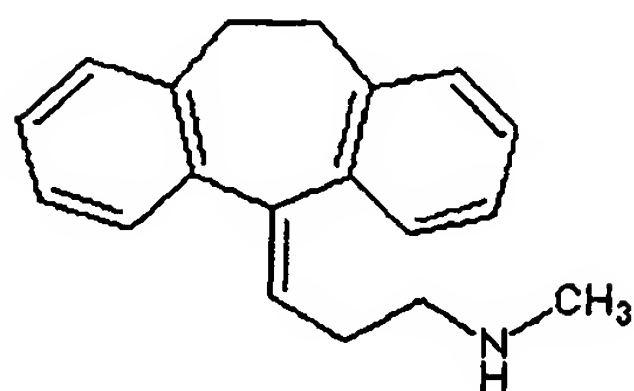
(B' 7b)



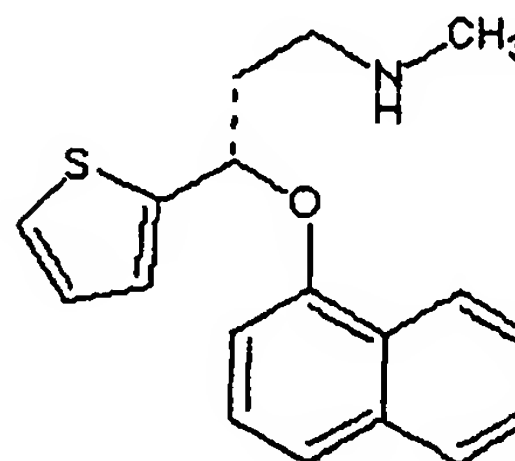
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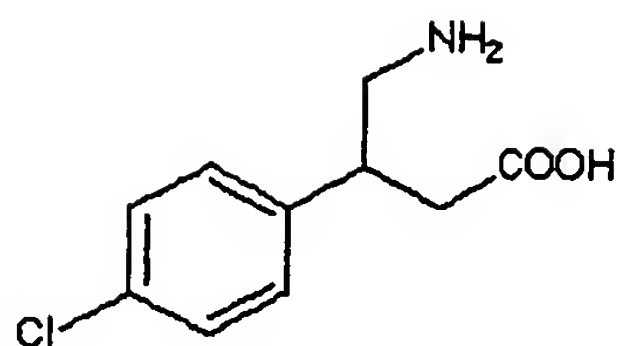
(B' 7d)



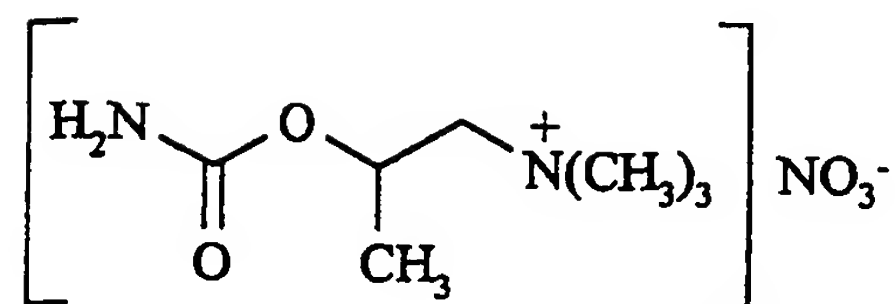
(B' 7e)



(B' 7f)



(B'8)



(B'9)

B'11) 3-(piperidin-1-yl)propyl 4-amino-5-chloro-2-methoxybenzoate (B'11a), 1-[4-amino-5-chloro-2-(3,5-dimethoxyphenyl)methyl oxy]-3-[1-[2-methylsulphonylamino]ethyl piperidin-4-yl]-1-propanone (B'11b), 2(1-piperidinyl)ethyl-1H-indol-3-carboxylate (B'11c), (S)-2-chloro-5-methoxy-4-[5-(2-piperidylmethyl)-1,2,4-oxadiazol-3-yl]aniline (B'11d).

The synthesis of the compounds belonging to the classes B'1)-B'9) are described in the volume The Merck Index 12a Ed.; the synthesis of compound B'1e) is described in EP 388,054; of compound B'1g) is described in EP 350,309, of compound B'1d) is described in EP 325,571. The synthesis of compound B'11a) is carried out as described in EP 501,322, of compound B'11b) as described in Br. J. Pharmacol. 1995, 115. 1087-1095, of compound B'11c) as described in EP 429,984.

The compounds inhibiting the phosphodiesterase C) salifiable with organic or inorganic acids are selected from the following: (C1) 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazol[4,3-d]-pyrimidin-5-yl)-phenyl]sulphoyl]-4-methyl-piperazine (Sildenafil), (C2) 2-(2-propyloxyphenyl)-8-azapurin-6-one (Zaprinst), (C3) 2,6-bis-(diethanolamino)-4,8-dipiperidine pyrimido [5,4-d]-pyrimidine (dipyridamol), (C4) 6-chloro-4-(1,3-dioxaindan-5-yl) methylamino-2(4-carboxy-1-piperidinyl)-quinazoline, (C5) N-(phenylmethyl)-1-ethyl-1H-pyrazol-[3,4-b]-quinolin-4-amine, (C6) 1-(2-chlorobenzyl)-3-isobutyryl-2-propyl-6-aminocarbonyl-indol, (C7) 1-benzyl-6-chloro-2-[1-[3-(imidazol-1-yl)propyl]indol-5-yl-amino carbonyl]benzimidazol, (C8) 2-(1-imidazolyl)-5-(phenyl)-4-(1,3-dioxaindan-5-yl)methyl aminopyrimidine, (C9) 6-ethynyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline, (C10) 1-cyclopentyl-3-ethyl-6-(2-propoxyphenyl)pyrazol[3,4-d]pyrimidin-4-one, (C11) 1-cyclopentyl-3-ethyl-6-(4-methoxybenzyl)-pyrazol-[3,4-d]-pyrimidin-4-one, (C12) 1,3-dimethyl-

6-(2-propoxy-5-methansulphonamidophenyl)-1,5-dihydro pyrazol[3,4-d]-pyrimidin-4-one, (C13) (6R, 12aR)-2,3, 6,7,12, 12a-hexahydro-2-methyl-6-(1,3-dioxan-5-yl)pyrazin [2',1':6,1] pyrido[3,4-b]indol-1,4-dione, (C14) 1-propyl-3-methyl-6-[2-propoxy-5-[(4'-methyl-1-pyrazinyl)sulphonamido] phenyl]-1,5-dihdropyrazol[3,4-d]pyrimidin-4-one, (C15) 3-(4-amino carbonyl-1-piperidinyl)-6-cyan-8-(3-chloro-4-methoxy-phthalazine, (C16) 2-(1-imidazolyl)-4-(1,3-dioxaindan-5-yl) methylamino-7,8-dihydro-5H-thiopyran[3,2-d]pyrimidine, (C17) 1-Cyclopentyl-3-ethyl-6-(3-ethoxypyrid-4-yl)-1H-pyrazolo[3,4-d] pyrimidin-4-one, (C18) 1-[3-[1-[(4-Fluorophenyl)methyl]-7,8-dihydro-8-oxo-1H-imidazo[4,5-g]quinazolin-6-yl]-4-propoxyphenyl] carboxamide.

Examples of organic salts of C) are oxalate, tartrate, maleate, succinate, citrate, glycinate, lysinate; examples of inorganic anions are nitrate, chloride, sulphate, phosphate. Nitrate salts are preferred.

The above compounds inhibiting the phosphodiesterases are synthesized as described in the following references: (C1): G.B. 92,480; (C2): DE 2,162,096; (C3): The Merck Index 12th Ed.; (C4): WO 9422855; (C5): WO 9628159; (C6): WO 9632379; (C7): WO 9703070; (C8): USP 5,525,604; (C9): USP 5,436,233; (C10): WO 9628448; (C11): WO 9628429; (C12): EP 636,626; (C13): WO 9519978; (C14): EP 636,626; (C15): WO 9605176; (C16): EP 728,759; (C17): US 5,294,612; (C18): J. Med. Chem 2000 43 1257-1263.

The nitrate salts of compounds B') and of compounds C) can be prepared as for example described in patent application WO 99/45004 in the name of the Applicant; the other salts of compounds C) with anions different from nitrate are prepared by methods known in the prior art, such as for example described in patent application WO 96/28448.

For the use according to the present invention one or more salts of the drugs of classes A)-C) are formulated in the corresponding pharmaceutical formulations according to well known techniques in the art, together with the usual excipients. The formulations can be for oral, parenteral use and are prepared as known in the prior art. See for example the volume "Remington's Pharmaceutical Sciences 15th Ed."

The dosages of the salts of the invention in their pharmaceutical compositions are the same, and generally lower

than those of their precursors of the above mentioned classes, said salts generally being more effective and better tolerated.

The following Examples illustrate but do not limit the scope of the invention.

EXAMPLE 1

Preparation of oxybutynin nitrate salt (B11)

To a solution of oxybutynin chloride (1.1 g, 2.82 mmoles) (B'11) in acetonitrile (25 ml) silver nitrate (0.48 g, 2.82 mmoles) dissolved in acetonitrile (10 ml) is added. The mixture is maintained under stirring for 30 minutes sheltered from light and at room temperature. The precipitate (AgCl) is filtered and the solution is concentrated under reduced pressure up to half of the initial volume. Ethyl ether (50 ml) is added. By cooling with ice a precipitate is separated which is filtered and washed with ethyl ether (3 X 5 ml). After drying 0.8 g of oxybutynin nitrate salt are obtained as an amorphous solid. Yield 68%.

Melting point 86-87°C.

Elementary analysis

Calculated %:	C	62.84	H	7.67	N	6.66
Found %:	C	62.67	H	7.66	N	6.70

EXAMPLE 2

Preparation of benzidamine nitrate salt (B'10g)

1) Preparation of benzidamine base

Benzidamine hydrochloride (3 g, 8.7 mmoles) (B'10g) is dissolved in an aqueous solution of sodium hydroxide (10% w/w, 45 ml) and the solution is extracted with ethyl acetate (3 X 50 ml). The joined organic phases are washed with water, anhydrified with sodium sulphate and the solvent evaporated under reduced pressure. An yellow oil formed by benzidamine free base is obtained.

¹H NMR (DMSO): 7.65-7.6 (2H, m); 7.45-7.2 (6H, m); 7.15 (1H, t); 5.45 (2H, s); 4.4 (2H, t); 2.4 (2H, t); 2.2 (6H, s); 2.0 (2H, m).

2) Preparation of benzidamine nitrate salt

To a solution of benzidamine (2.5 g, 8.1 mmoles) in acetonitrile (15 ml), cooled at 0 °C, nitric acid 65% (0.560 ml, 8.1 mmoles) is added. The mixture is maintained under stirring at 0°C for 30 minutes, the temperature is let reach the room temperature and the mixture is maintained under

stirring for 1 hour. After addition of ethyl ether (10 ml) a white solid is separated which is filtered and washed with ethyl ether. After drying 2.6 g of benzidamine nitrate salt are obtained. Melting point 143-144°C.

Elementary analysis

Calculated %:	C	61.29	H	6.49	N	15.04
Found %:	C	60.93	H	6.45	N	14.97

EXAMPLE 3

Preparation of papaverine nitrate salt (B'10e)

1) Preparation papaverine base

Papaverine hydrochloride (3 g, 8 mmol) (B'10e) is dissolved in an aqueous solution of sodium hydroxide (10% w/w, 50 ml) and the solution is extracted with chloroform (3 X 50 ml). The joined organic phases are washed with water, anhydriified with sodium sulphate and the organic solvent evaporated under reduced pressure. Papaverine base (2.7 g) is obtained as an amorphous solid.

¹H NMR (DMSO): 8.4 (1H, d); 7.6 (2H, d); 7.4 (1H, s); 6.8 (2H, m); 4.5 (2H, s); 3.9 (6H, d); 3.7 (6H, d).

2). Preparation of papaverine nitrate salt

To a solution of papaverine (2.6 g, 7.6 mmol) in acetonitrile (100 ml), cooled at 0 °C, nitric acid 65% (0.560 ml, 8.1 mmol) is added. The mixture is maintained under stirring at 0°C for 30 minutes, it is let reach the room temperature and the mixture is maintained under stirring for 2 hours. The formed precipitate is filtered and washed with acetonitrile. After drying 2.3 g of papaverine nitrate salt are obtained.

Elementary analysis

Calculated %:	C	59.69	H	5.51	N	6.96
Found %:	C	58.68	H	5.38	N	6.86

EXAMPLE 4

Preparation of phenylpropanolamine nitrate salt (B'4c)

To a solution of phenylpropanolamine hydrochloride (2 g, 10.75 mmol) (B'4c) in acetonitrile (50 ml) silver nitrate (1.83 g, 10.77 mmol) is added. The salt preparation is carried out following the procedure described in Example 1. The phenylpropanolamine nitrate salt is obtained as an amorphous solid.

Elementary analysis

Calculated %:	C	50.46	H	6.59	N	13.08
Found %:	C	50.60	H	6.62	N	13.12

EXAMPLE 5

Preparation of pinacidil nitrate salt (B'3)

To a solution of pinacidil (3 g, 12.23 mmol) (B'3) in acetonitrile (100 ml), cooled at 0°C, nitric acid 65% (0.850 ml, 12.27 mmol) is added. The mixture is maintained under stirring at 0°C for 30 minutes. At the end it is let reach the room temperature and the mixture is maintained under stirring for 2 hours. After addition of ethyl ether a precipitate forms which is filtered and washed with ethyl ether (3 X 20 ml). After drying 2.3 g of pinacidil nitrate salt are obtained. Yield 60%.

Elementary analysis

Calculated %:	C	50.64	H	6.54	N	27.26
Found %:	C	50.73	H	6.62	N	27.19

EXAMPLE 6

Preparation of terodiline nitrate salt (B'1p)

Terodiline hydrochloride (2 g, 6.3 mmol) (B'1p) is dissolved in an aqueous solution of sodium hydroxide (10% w/w, 35 ml) and the solution extracted with ethyl acetate (3 X 50 ml). The joined organic phases are washed with water, anhydriified with sodium sulphate and the organic solvent evaporated under reduced pressure. The residue is dissolved in acetonitrile (15 ml) and the solution is cooled at 0°C. Nitric acid 65% (0.440 ml, 6.35 mmol) is added. The mixture is maintained under stirring at 0°C for 30 minutes, then it is let reach the room temperature and the mixture is maintained under stirring for 1 hour. By adding ethyl ether (10 ml) a white solid is separated which is filtered and washed with ethyl ether. After drying 1.2 g of terodiline nitrate salt are obtained. Yield 55%.

Elementary analysis

Calculated %:	C	69.74	H	8.19	N	8.13
Found %:	C	69.80	H	8.25	N	8.09

EXAMPLE 7

Preparation of propantheline nitrate salt (B'1a)

The compound is prepared starting from a solution of propantheline bromide (3 g, 6.7 mmol) (B'1a) in acetonitrile (80 ml), adding silver nitrate (1.3 g, 7.06 mmol)

dissolved in acetonitrile (10 ml), and following the procedure described in Example 1. After drying, propantheline nitrate salt is obtained as an amorphous solid (1.4 g). Yield 48%.

Elementary analysis

Calculated %:	C	64.02	H	7.24	N	6.49
Found %:	C	64.11	H	7.27	N	6.45

EXAMPLE 8

Preparation of flavoxate nitrate salt (B'1o)

The compound is prepared starting from a solution of flavoxate hydrochloride (2 g, 4.7 mmoles) (B'1o) in acetonitrile (50 ml) adding a silver nitrate solution (0.800 g, 4.76 mmoles) in acetonitrile (10 ml) and following the procedure described in Example 1. After drying flavoxate nitrate salt is obtained as an amorphous solid (1.1 g). Yield 50%.

Elementary analysis

Calculated %:	C	63.42	H	5.77	N	6.16
Found %:	C	63.52	H	5.98	N	6.20

EXAMPLE 9

Preparation of dicyclomine nitrate salt (B'1m)

The compound is prepared starting from a solution of dicyclomine hydrochloride (2 g, 5.78 mmoles) (B'1m) in acetonitrile (50 ml) adding silver nitrate (0.990 g, 4.76 mmoles) dissolved in acetonitrile (10 ml) and following the procedure described in Example 1. After drying dicyclomine nitrate salt is obtained as an amorphous solid (1.3 g). Yield 60%.

Elementary analysis

Calculated %:	C	61.26	H	9.74	N	7.52
Found %:	C	61.19	H	9.69	N	7.58

PHARMACOLOGICAL EXAMPLES

The activity in the urinary incontinence of the compounds according to the present invention has been evaluated in an experimental model of inhibition of the bladder contraction.

The degree of the relaxation induced in the urinary bladder is a measure of the inhibitory action of the urinary incontinence of the drugs described in the present application.

Guinea-pigs of male sex having an average weight equal to 300-500 g were sacrificed and bled. The urinary bladder was removed and prepared for determining the myorelaxing activity in vitro, according to the method described by L.Nilvenbrant, Eur.J.Pharmacol. 327,195-207, 1997.

The obtained tissue strips were contracted with carbacol 10^{-6} M in physiological solution and the relaxation was determined in the presence of the compounds indicated in Table 1 at the concentrations mentioned therein. The 2-(acetyloxy) benzoic acid 6-(nitroxymethyl)-2-methylpyridyl ester hydrochloride was prepared according to Example 1 of patent application PCT/EP 00/01454 (NCX 4050).

The sildenafil nitrate salt was prepared as described in patent application WO 99/67231 (Ex. 3).

In Table 1 the results are expressed as a percentage of the maximum inhibition of the contractions induced by carbacol 10^{-6} M and they show that the compounds of the present invention are active in the urinary incontinence since they are able to exert a significant relaxing effect on the urinary guinea-pig bladder, which in the case of the nitrate salts of the drugs used in the incontinence is higher than that of the precursors.

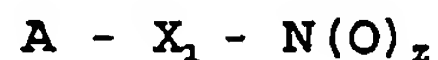
Table 1

Activity in the urinary incontinence of the compounds NCX 4050, sildenafil nitrate, sildenafil citrate, oxybutynin nitrate and oxybutynin hydrochloride in an experimental model in vitro of strips of urinary guinea-pig bladder contracted with carbacol		
Treatment	Concentration (M)	Urinary bladder contraction %
Placebo	-----	100
NCX 4050	3×10^{-5}	71
Sildenafil Nitrate	3×10^{-5}	31
Sildenafil Citrate	3×10^{-5}	52
Oxybutynin Hydrochloride (Comp)	10^{-6}	30
Oxybutynin Nitrate	10^{-6}	0

CLAIMS

1. Use in the incontinence of one or more of the following classes of drugs selected from the following:

A) nitric oxide donor drugs, salified and non salified of formula

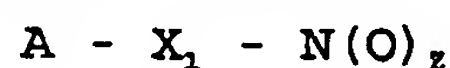


wherein A, X_1 , Z have the meaning defined below;

B') nitrate salts of drugs used for the incontinence and which do not contain in the molecule a nitric oxide donor group;

C) organic or inorganic salts of compounds inhibiting phosphodiesterases;

in the compounds of general formula:

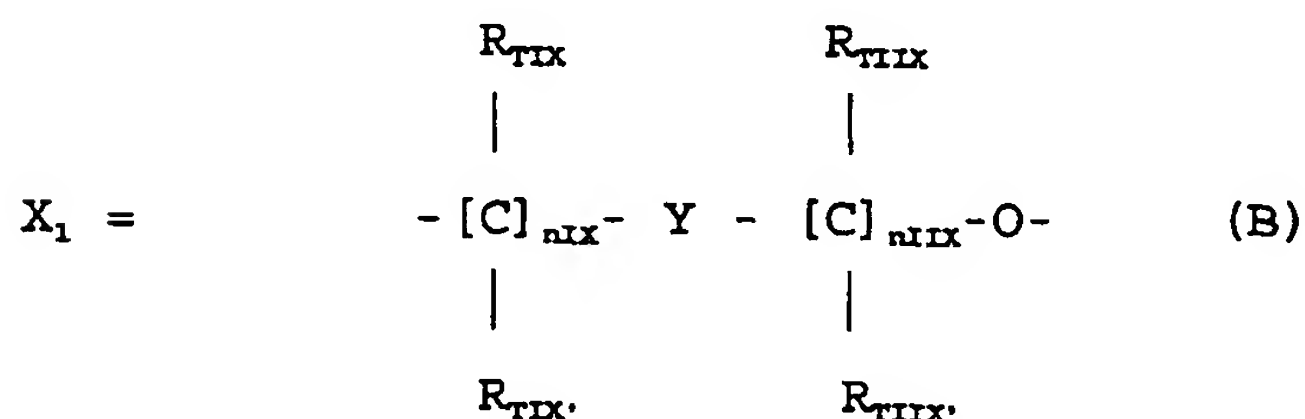


z is an integer and is 1 or 2, preferably 2;

A = $R(COX_u)_t$ and wherein t is an integer 0 or 1; u is 0 or 1;

X = O, NH, NR_{1c} wherein R_{1c} is a linear or branched C_1 - C_{10} alkyl;

X_1 is the following bivalent linking group:



wherein:

nIX is an integer in the range 0-3;

nIIX is an integer in the range 1-3;

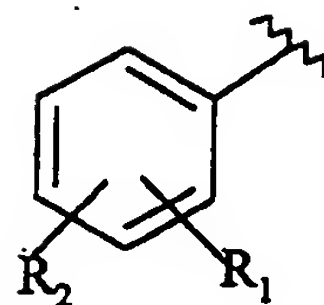
R_{TIX} , $R_{TIX'}$, R_{TIIIX} , $R_{TIIIX'}$, equal to or different from each other are H or a linear or branched C_1 - C_4 alkyl;

Y is a heterocyclic ring containing one or two nitrogen atoms, optionally one oxygen or sulphur atom, said saturated, unsaturated or aromatic ring having 5 or 6 atoms;

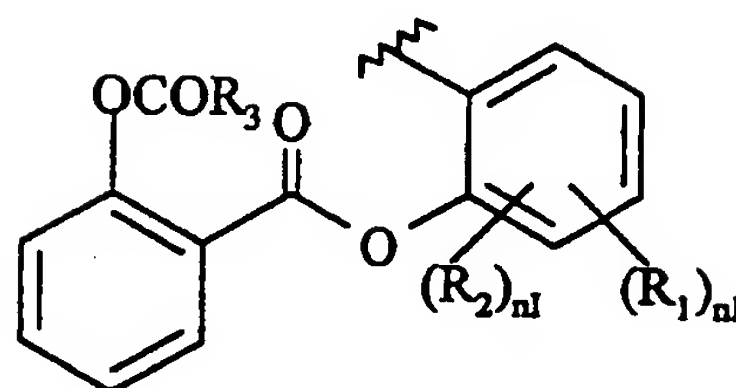
R of the radical A of formula $A - X_1 - N(O)_z$ is selected from the following groups:

Group I) wherein $t = 1$ and $u = 1$

Ia)



Ib)



wherein:

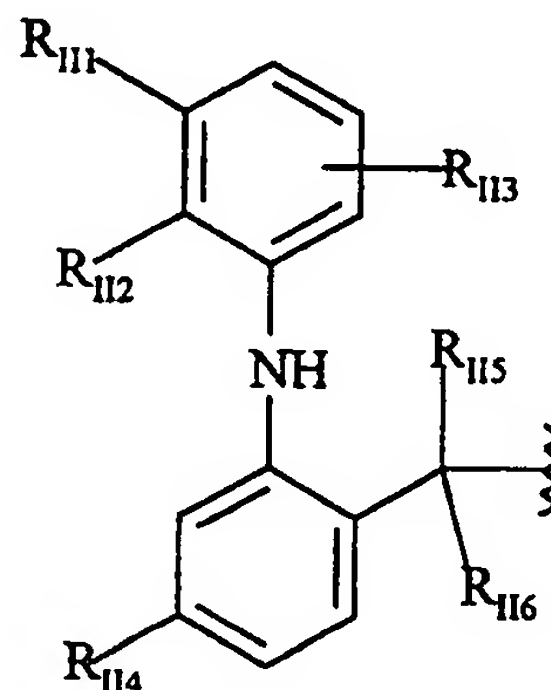
R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or a linear or branched C_3 - C_5 alkyl, or the residue of a heterocycle having only one ring having 5 or 6 atoms which can be aromatic, partially or totally hydrogenated, containing one or more heteroatoms independently selected from O, N and S;

R_2 is hydrogen, hydroxy, halogen, linear or branched C_1 - C_4 alkyl, linear or branched C_1 - C_4 alkoxy; a linear or branched C_1 - C_4 perfluoroalkyl, for example trifluoromethyl; nitro, amino, mono- or di- (C_{1-4}) alkylamino;

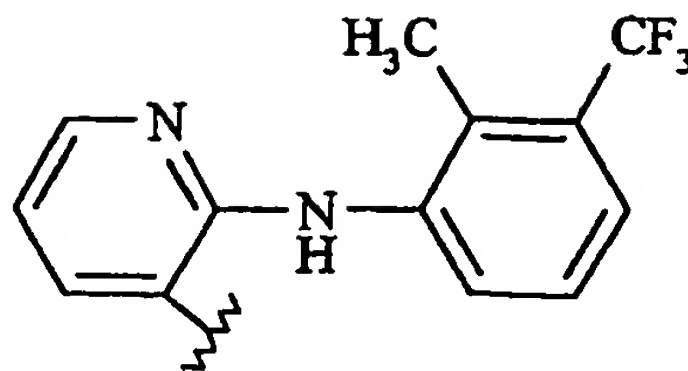
nI is an integer 0 or 1;

group II) wherein $t = 1$, $u = 1$

IIa)



IIb)



wherein:

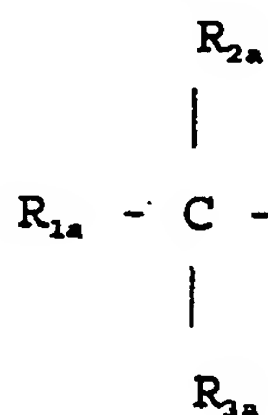
R_{II5} is H, linear or branched when possible C_1 - C_3 alkyl;

R_{II6} has the same meaning as R_{II5} , or when R_{II5} is H it can be benzyl;

R_{II1} , R_{II2} and R_{II3} can independently be hydrogen, linear or branched when possible C_1 - C_6 alkyl, or linear or branched when possible C_1 - C_6 alkoxy, or Cl, F, Br;

R_{II4} is R_{II1} or bromine;

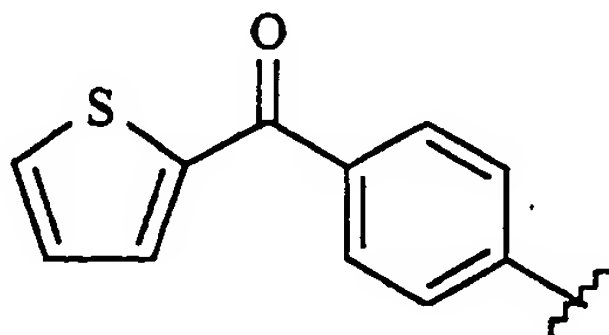
IIb) is the residue of the 2-[(2-methyl-3-(trifluoromethyl)phenyl)amino]-3-pyridincarboxylic acid and when the -COOH group is present the compound is known as flunixin; group III) wherein $t = 1$, $u = 1$ and R is



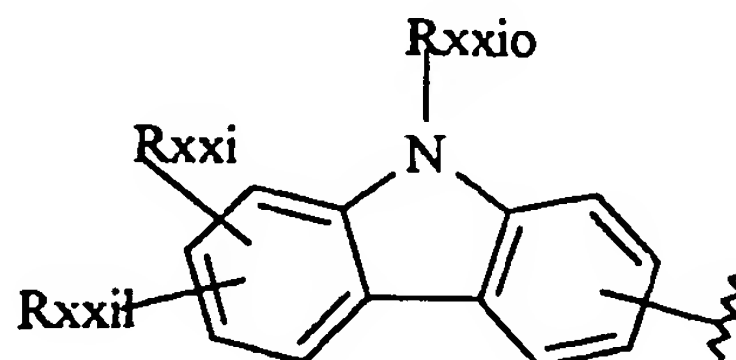
wherein:

R_{2a} and R_{3a} are H, linear or branched when possible, substituted or not, C_1 - C_{12} alkyl or allyl, with the proviso that if one of the two is allyl the other is H; preferably R_{2a} is H, C_1 - C_4 alkyl, R_{3a} is H;

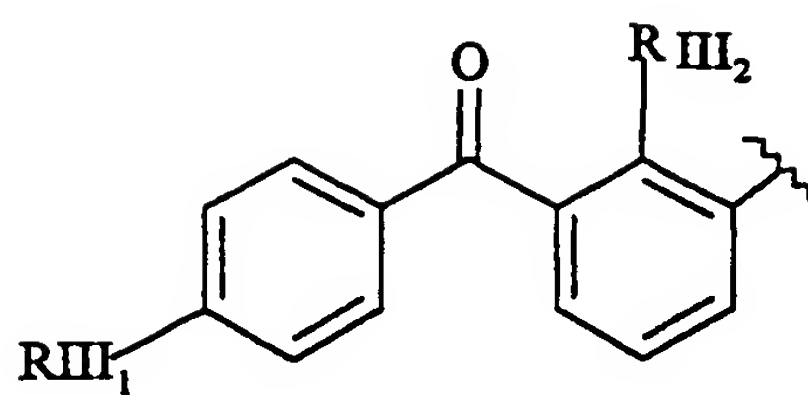
R_{1a} is selected from



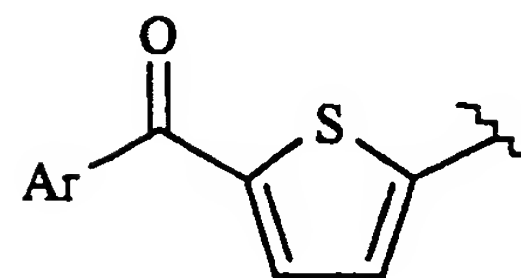
(II)



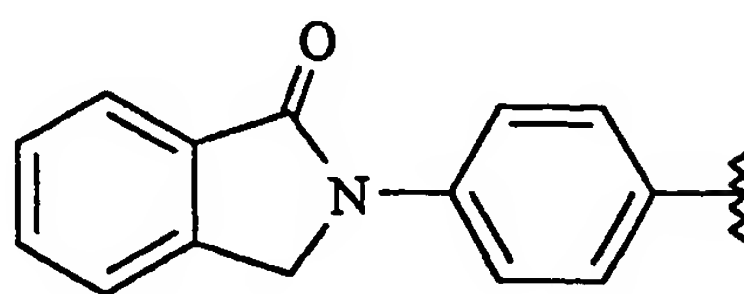
(XXI)



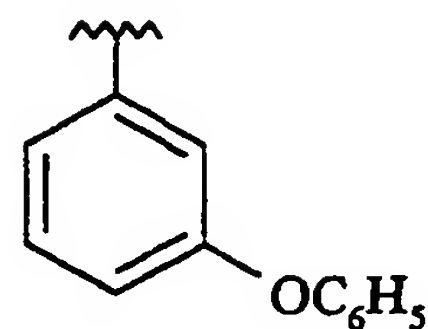
(IV)



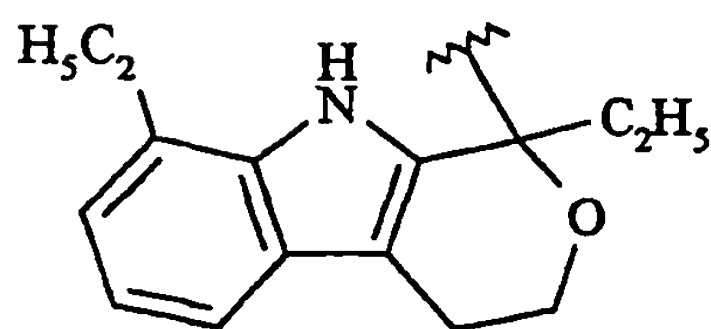
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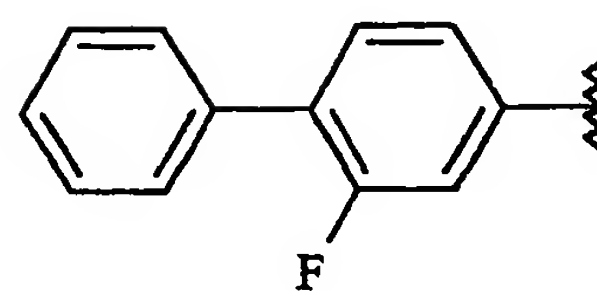
(VI)



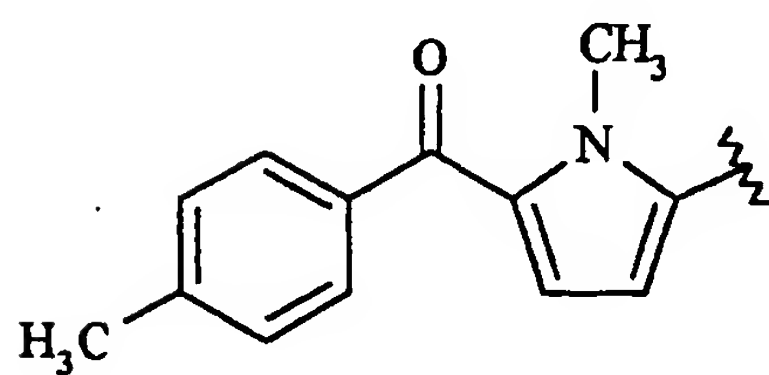
(VII)



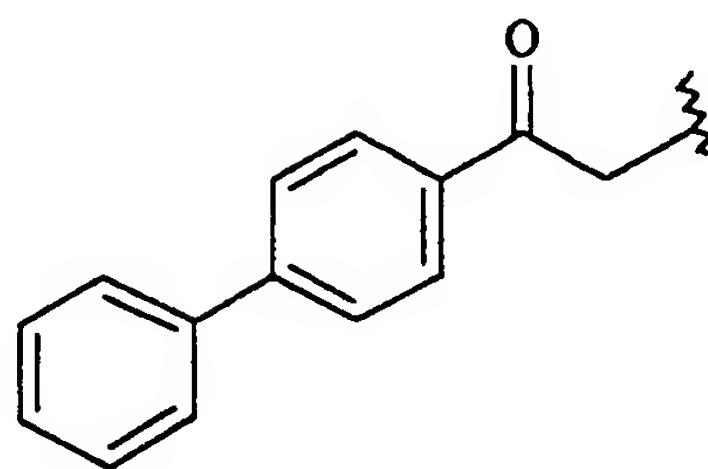
(VIII)



(IX)

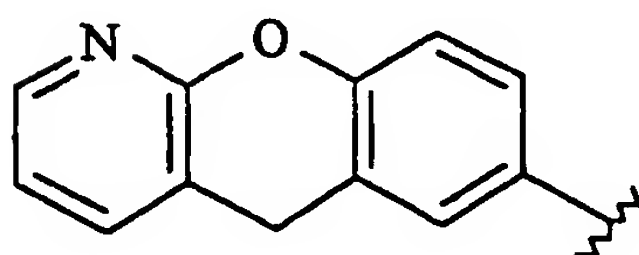


(X)

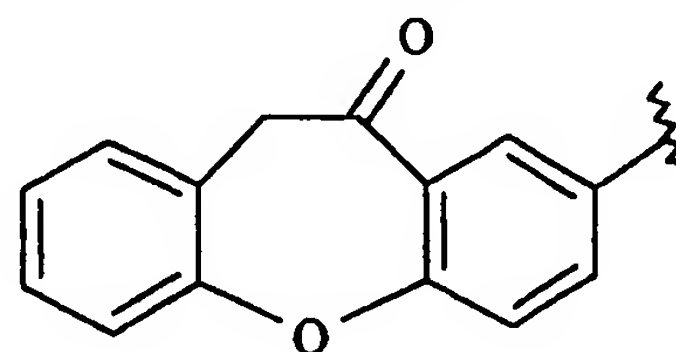


(III)

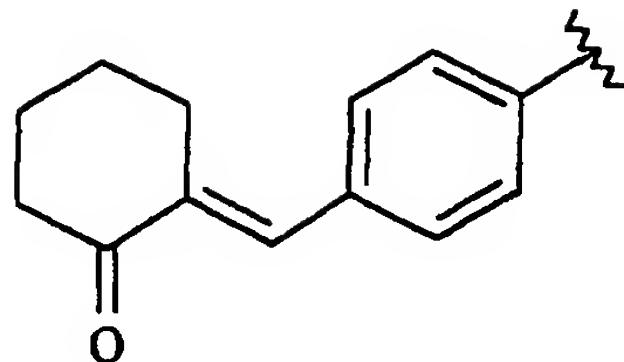
IIID) R_{1a} corresponds to the following formulas:



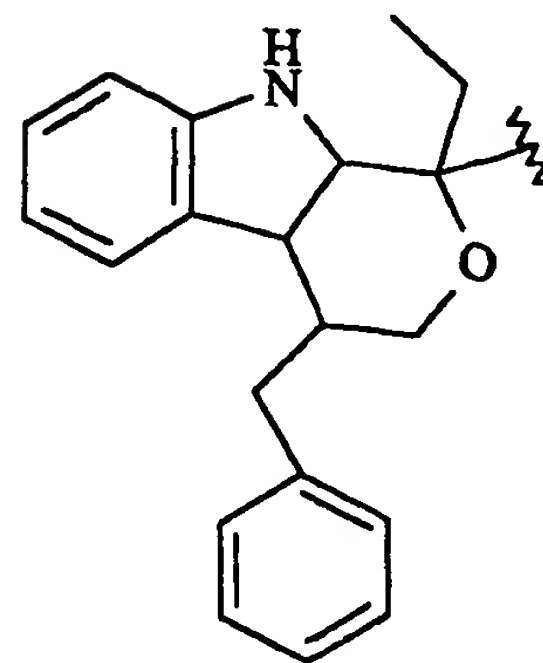
(IIIa)



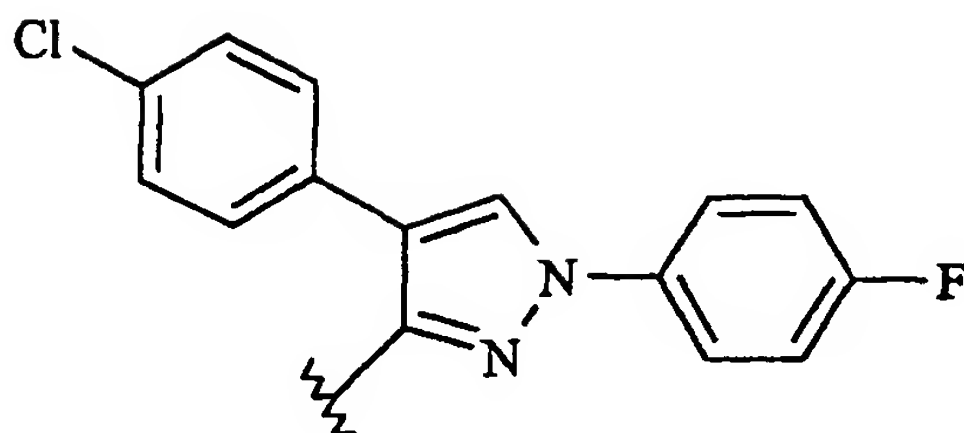
(XXX)



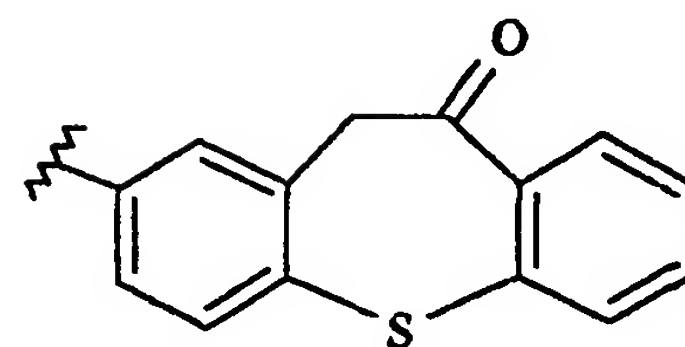
(XXXI)



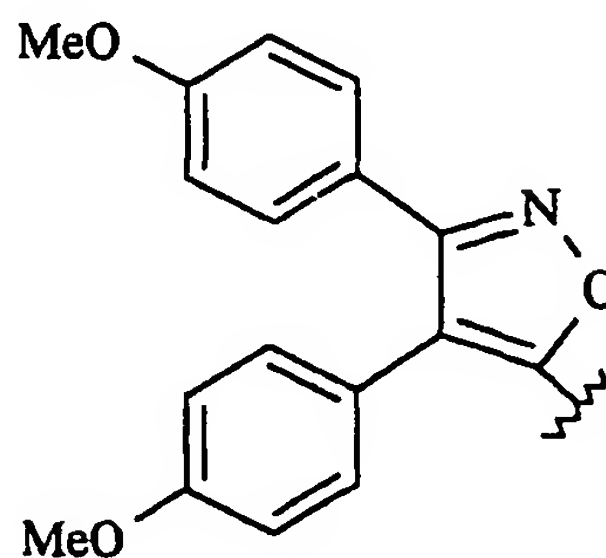
(XXXII)



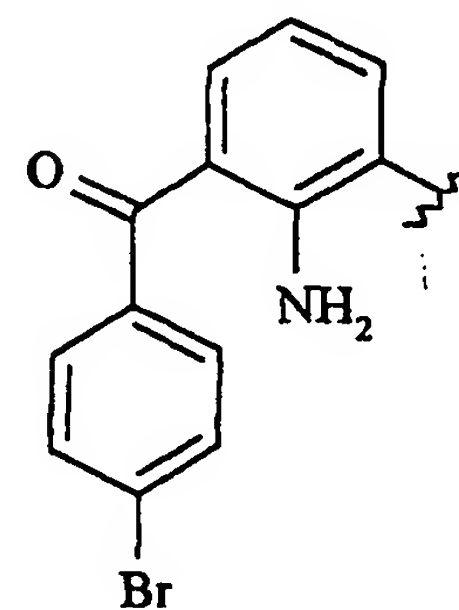
(XXXIII)



(XXXVI)



(XXXVII)



(XII)

wherein the meanings are the following:

- when R_{1a} is as defined in formula (IV), Ketoprofen residue: R_{III1} is H, SR_{III3} wherein R_{III3} contains from 1 to 4 carbon atoms, linear or branched when possible; R_{III2} is H, hydroxy;
- when R_{1a} is as defined in formula (XXI), carprofen residue: R_{xx10} is H, linear or branched when possible alkyl from 1 to 6 carbon atoms, C_1-C_6 alkoxy carbonyl linked to a C_1-C_6 alkyl, C_1-C_6 carboxyalkyl, C_1-C_6

alkanoyl, optionally substituted with halogens, benzyl or halobenzyl, benzoyl or halobenzoyl;

R_{xx1} is H, halogen, hydroxy, CN, C_1-C_6 alkyl optionally containing OH groups, C_1-C_6 alkoxy, acetyl, benzyloxy, SR_{xx12} wherein R_{xx12} is C_1-C_6 alkyl; C_1-C_3 perfluoroalkyl; C_1-C_6 carboxyalkyl optionally containing OH groups, NO_2 , amino; sulphamoyl, di-alkyl sulphamoyl with C_1-C_6 alkyl, or difluoroalkylsulphonyl with C_1-C_3 alkyl;

R_{xx11} is halogen, CN, C_1-C_6 alkyl containing one or more OH groups, C_1-C_6 alkoxy, acetyl, acetamido, benzyloxy, SR_{xx13} being R_{xx13} as above defined, C_1-C_3 perfluoroalkyl, hydroxy, C_1-C_6 carboxyalkyl, NO_2 , amino, mono- or di-alkyl-amino C_1-C_6 ; sulphamoyl, di-alkyl sulphamoyl C_1-C_6 , or di-fluoroalkylsulphamoyl as above defined; or R_{xx1} together with R_{xx11} is a C_1-C_6 alkylene dioxy;

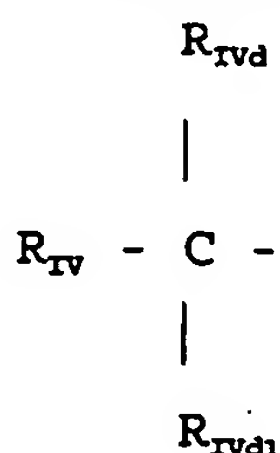
- when R_{1a} is as defined in formula (XXXV) tiaprofenic acid residue:

Ar is phenyl, hydroxyphenyl optionally mono or polysubstituted with halogen, alkanoyl and alkoxy C_1-C_6 , C_1-C_6 , preferably C_1-C_3 , trialkyl, cyclopentyl, cyclohexyl, cycloheptyl, heteroaryl, preferably thienyl, furyl optionally containing OH, pyridyl;

- when R_{1a} is as defined in formula (II), suprofen residue, wherein R_{3a} is H, R_{2a} is methyl and $X = O$;
- when R_{1a} is as defined in formula (VI), R is the residue of indoprofen when $R_{2a} = H$ and $R_{3a} = CH_3$; of indobufen when R_{2a} is equal to H and $R_{3a} = C_2H_5$; $X = O$;
- when R_{1a} is as defined in formula (VIII), R is the etodolac residue when $R_{2a} = R_{3a} = H$ and $X = O$;
- when R_{1a} is as defined in formula (VII), R is the fenoprofen residue when $R_{3a} = H$, $R_{2a} = CH_3$ and $X = O$;
- when R_{1a} is as defined in formula (III), R is the fenbufen residue when $R_{2a} = R_{3a} = H$ and $X = O$;
- when R_{1a} is as defined in formula (IX), R is the flurbiprofen residue when $R_{3a} = H$, $R_{2a} = CH_3$, $X = O$;

- when R_{1a} is as defined in formula (X) R is the tolmetin residue when $R_{2a} = R_{3a} = H$, $X = O$;
- in group IIID) R_{1a} corresponds to the following formulas:
- IIIa), when $R_{2a} = H$ and $R_{3a} = CH_3$, the pranoprofen residue is obtained: α -methyl-5H-[1]benzopyran-[2,3-b]pyridin-7-acetic acid; the preferred compound has $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$;
 - (XXX), when $R_{2a} = H$ and $R_{3a} = CH_3$, the bermoprofen residue is obtained: dibenz[b,f]oxepin-2-acetic acid;
 - (XXXI), when $R_{2a} = H$ and $R_{3a} = CH_3$, R is the radical of the CS-670 compound: 2-[4-(2-oxo-1-cyclohexyliden methyl) phenyl]propionic acid;
 - (XXXII), when $R_{2a} = R_{3a} = H$ the Pemedolac residue is obtained;
 - (XXXIII), when $R_{2a} = R_{3a} = H$ the pyrazolac residue is obtained: 4-(4-chlorophenyl)-1-(4-fluoro phenyl)-3-pyrazolic acid;
 - (XXXVI), when $R_{2a} = H$, $R_{3a} = CH_3$, the zaltoprofen residue is obtained; when the residue is saturated with an hydroxyl or amino group, or with the carboxylic function the compounds are known as dibenzothiepine derivatives;
 - (XXXVII), when $R_{2a} = R_{3a} = H$ the mofezolac residue is obtained: 3,4-di(p-methoxyphenyl)isoxazol-5-acetic acid;
 - (XII), when $R_{2a} = R_{3a} = H$ the bromfenac residue is obtained: 2-amino-3-(4-bromobenzoyl)benzeneacetic acid;

in group IV) wherein $t = 1$, $u = 1$, R is

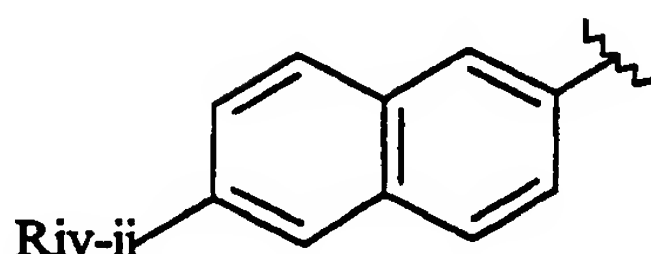


wherein:

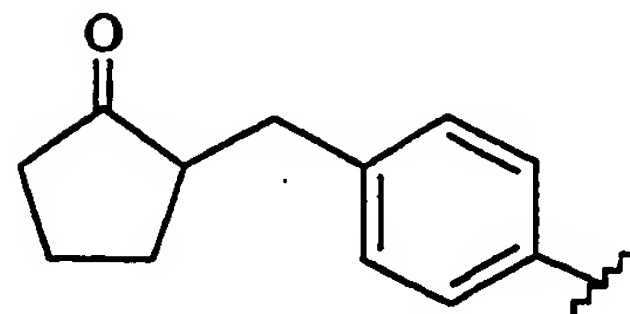
R_{IVd} and R_{IVd1} are at least one H and the other a linear or branched C_1 - C_6 , preferably C_1 and C_2 alkyl, or difluoroalkyl with the alkyl from 1 to 6 carbon atoms, C_1 is

preferred, or R_{IVd} and R_{IVd1} form together a methylene group;

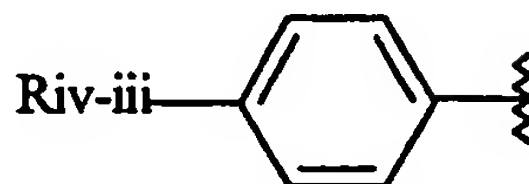
R_{IV} has the following meaning:



(II)



(X)



(III)

wherein the compounds of group IV) have the following meanings:

- in formula (II):

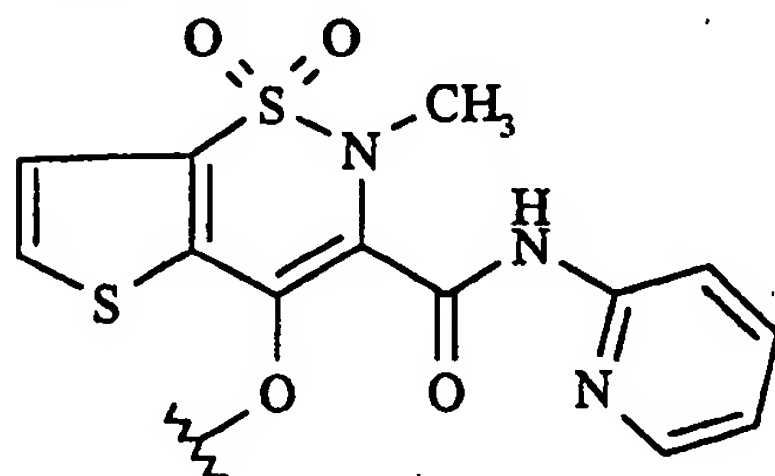
R_{IV-ii} is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_7 alkoxyethyl, C_1-C_7 trifluoroalkyl, vinyl, ethynyl, halogen, C_1-C_6 alkoxy, difluoroalkoxy, with the C_1-C_7 alkyl, C_1-C_7 alkoxyethoxy, alkylthio methoxy with the C_1-C_7 alkyl, alkyl methylthio with the C_1-C_7 alkyl, cyan, difluoromethylthio, phenyl- or phenylalkyl substituted with C_1-C_6 alkyl.

- formula (X) loxoprofen residue;

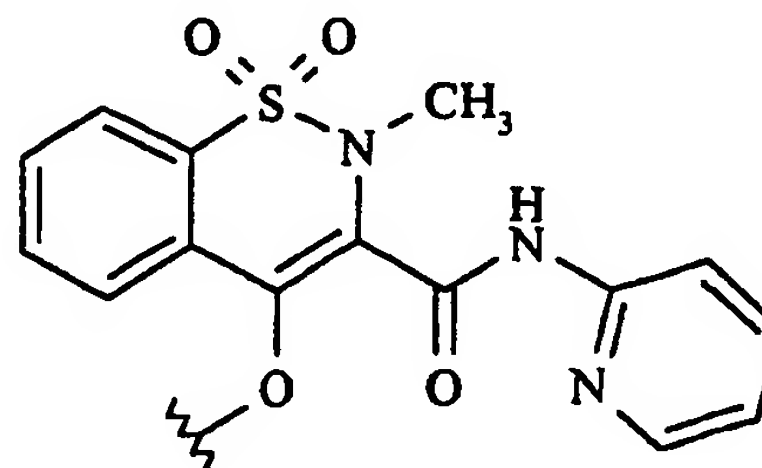
- in formula (III):

R_{IV-iii} is a C_2-C_8 alkyl, optionally branched when possible, C_2 and C_3 alkoxy, allyloxy, phenoxy, phenylthio, cycloalkyl from 5 to 7 carbon atoms, optionally substituted in position 1 by a C_1-C_2 alkyl;

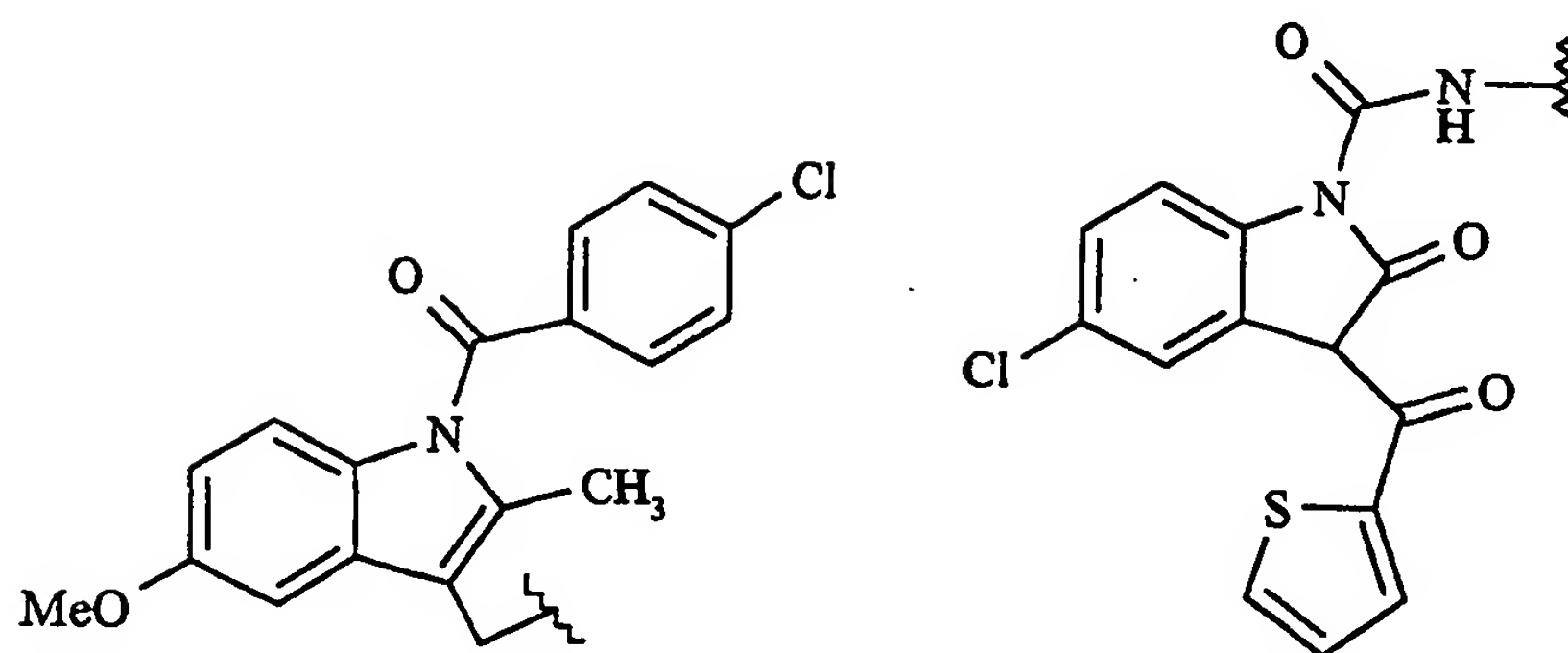
Group V)



(VII)

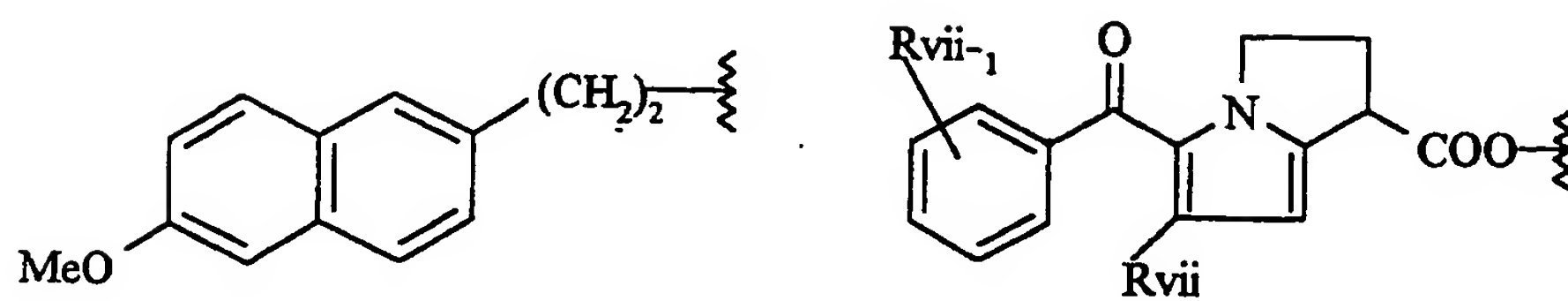


(IX)



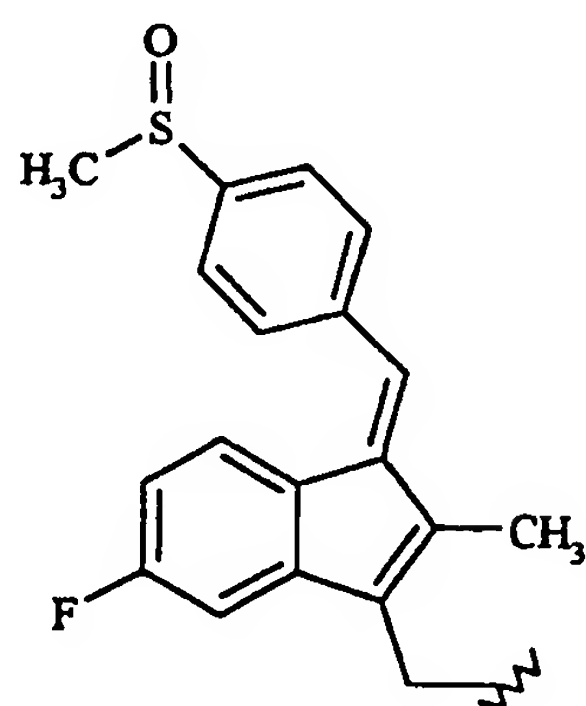
(IV)

(V)



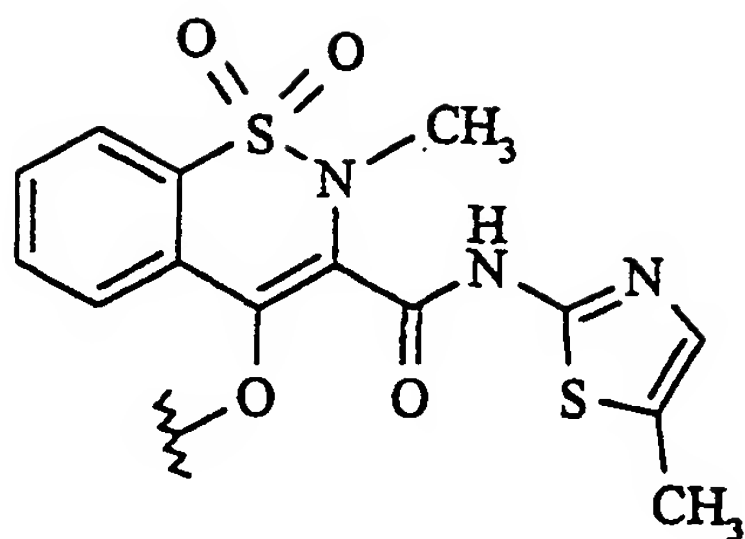
(III)

(II)

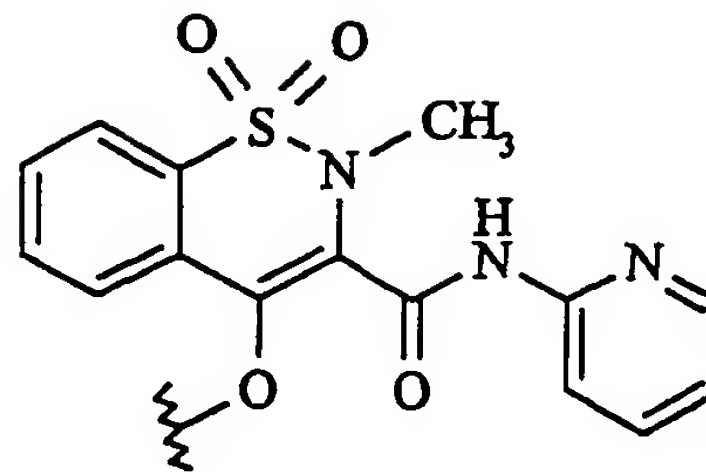


(LX)

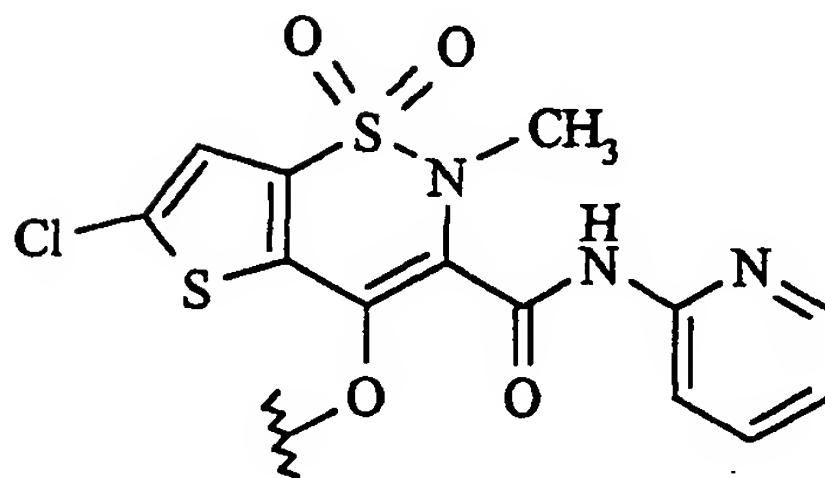
Group VE)



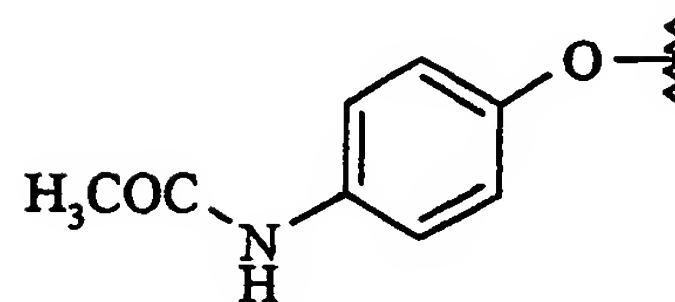
(X)



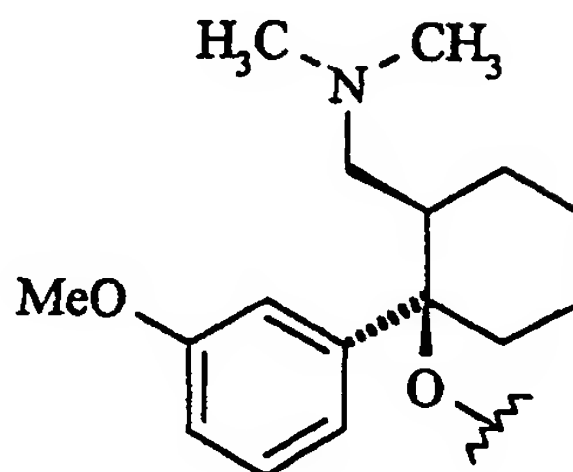
(XI)



(XIII)



(XXXX)

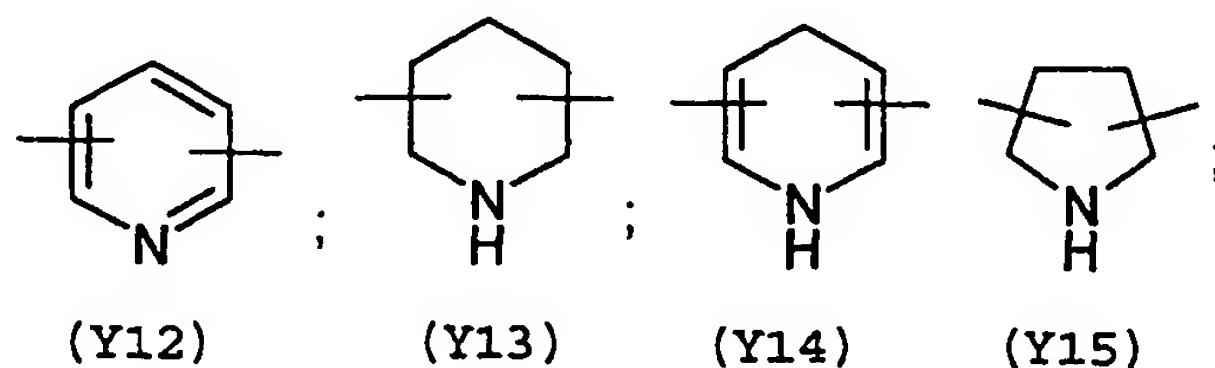
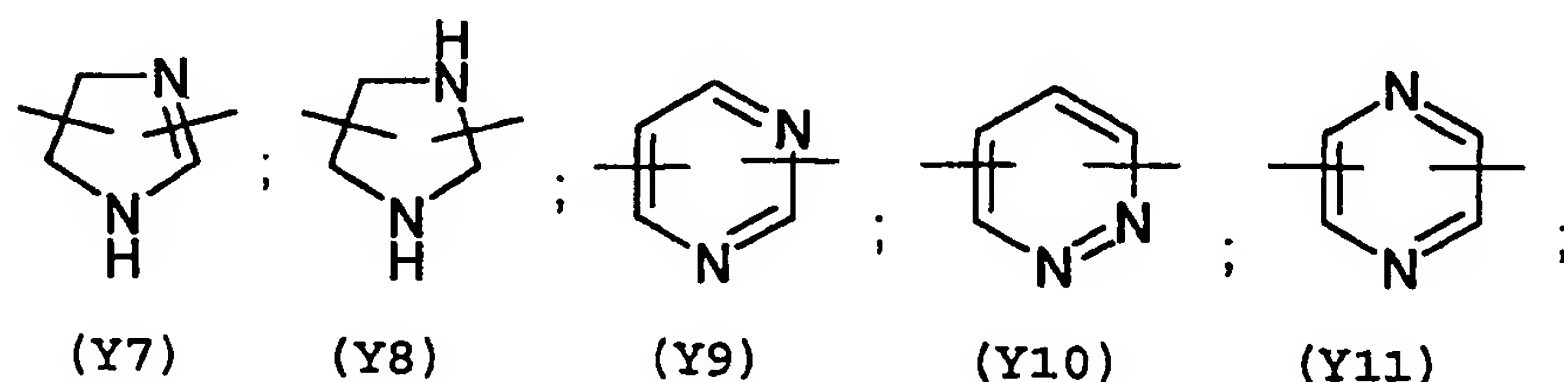
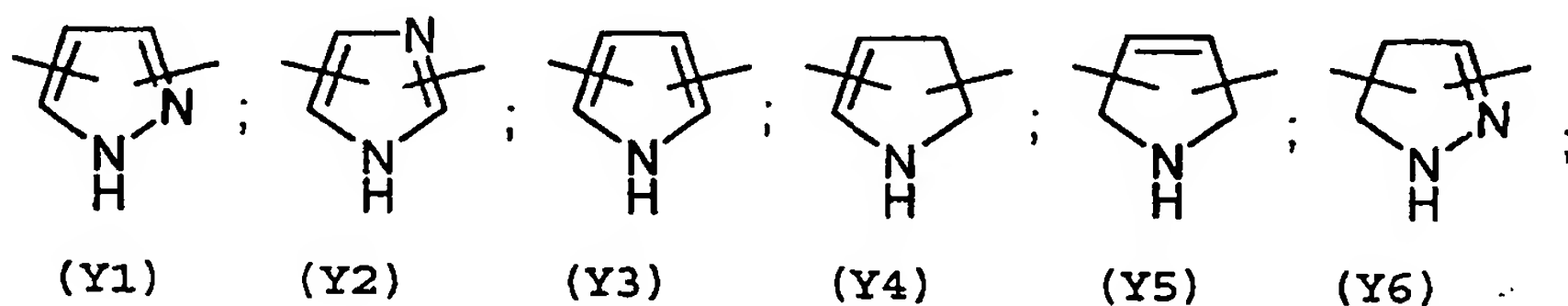


(XXXXI)

In group V):

- when R is formula (II), R_{VII} is H or a linear or branched C_1 - C_4 alkyl;
 R_{VII-1} is R_{VII} , or a linear or branched C_1 - C_4 alkoxy;
Cl, F, Br; the position of R_{VII-1} being ortho, or metha, or para;
- when R is formula (V),
of which the residue of the known tenidap has been indicated;
- when R is formula (V) A = R and t = 0,
- when R is formula (VII), A is RCO, t = 1 u = 0 or A is R and t = 0;
- when R is formula (IX), A = R and t = 0, or A = RCO with t = 1 and u = 0;

- when R is formula (III) $A = \text{RCOO}$, $t = 1$ and $u = 0$ or 1; or $t = 0$ and $A = R$;
 - when R is formula (IV) $A = \text{RCOO}$, $t = 1$ and $u = 1$;
 - when R is formula (LX) and in $(\text{COX}_u)_t$, $u = t = 1$ and X is oxygen, the precursor compound is sulindac;
 - when R is formula (X) it is the meloxicam residue;
 - when R is formula (XI) the residue is known as ampiroxicam when the termination is $-\text{CH}(\text{CH}_3)\text{OCOC}_2\text{H}_5$;
 - when R is formula (XIII) and the valence is saturated with H, the residue derives from lornoxicam;
 - when R is formula (XXXX) and the valence is saturated with H the compound is known as paracetamol;
 - when R is formula (XXXXI) and the valence is saturated with H the compound is known as tramadol.
2. Use according to claim 1, wherein Y is selected from the following:



3. Use according to claim 2, wherein Y is Y12 (pyridyl) substituted in position 2 and 6.
4. Use according to claims 1-3, wherein in the compounds A) of formula $\text{A-X}_z\text{-N(O)}_n$, z is 2 and nIX and nIIX in formula

(B) of X_1 are integers equal to 1 and R_{TIX} , $R_{TIX'}$, R_{TIXX} , $R_{TIXX'}$ are equal to H.

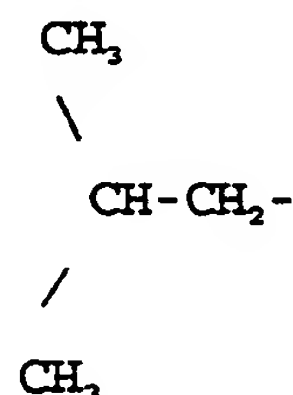
5. Use according to claims 1-4, wherein in the compounds of formula A) $A-X_1-N(O)_t$, R, X, u and t of formula A = $R(COX_u)_t$, and Y in formula (B) of X_1 , have the following meanings:

- when R is selected from group I), in the compounds of formula Ia) X is equal to O or NH, R_1 is acetoxy, preferably in ortho position with respect to -CO-, R_2 is hydrogen; in X_1 $R_{TIX} = R_{TIX'} = R_{TIXX} = R_{TIXX'} = H$, $n_{IX} = n_{IIX} = 1$ and Y is an aromatic ring having 6 atoms, containing one nitrogen atom, said aromatic ring having the two free valences in position 2 and 6; in the compounds of formula Ib) $R_3 = CH_3$, $nI = 0$, X is equal to O, X_1 is as above defined for Ia); in this case Ib) is the residue of the acetylsalicylsalicylic acid;
- when R is selected in group II) in formula IIA R_{IIX1} , R_{IIX4} are hydrogen and R_{IIX2} and R_{IIX3} are chlorine in ortho position with respect to NH; R_{IIX5} and R_{IIX6} are H, X is equal to O, and X_1 is as above defined for the compounds of formula Ia);
- when R is selected in group III),
- when R_{1a} is as defined in formula (IV) R_{IIX1} and R_{IIX2} are H, R_{3a} is H, and R_{2a} is methyl, X = O;
- when R_{1a} is as defined in formula (XXI) R_{XX10} is H, the linking group is in position 2, R_{XX1} is H, R_{XX11} is chlorine and it is in para position with respect to nitrogen;
- when R_{1a} is as defined in formula (XXXV) Ar is phenyl, R_{3a} is H, R_{2a} is methyl and X is O; R_{3a} is H, R_{2a} is methyl and X is O;
- when R_{1a} is as defined in formula IIIa), $R_{2a} = H$, $R_{3a} = CH_3$, u = 1 and X = O;
- when R_{1a} is as defined in formula (XXX) $R_{2a} = H$, $R_{3a} = CH_3$, u = 1 and X = O;
- when R_{1a} is as defined in formula (XXXI), $R_{2a} = H$, $R_{3a} = CH_3$, u = 1 and X = O;
- when R_{1a} is as defined in formula (XXXII), $R_{2a} = R_{3a} = H$, u = 1 and X = O;

- when R_{1a} is as defined in formula (XXXIII), $R_{2a} = R_{3a} = H$, $u = 1$ and $X = O$;
- when R_{1a} is as defined in formula (XXXVI), $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$;
- when R_{1a} is as defined in formula (XXXVII), $R_{2a} = R_{3a} = H$, $t = 1$ and $X = O$;
- when R_{1a} is as defined in formula (XII), $R_{2a} = R_{3a} = H$, $u = 1$, $t = 1$, $X = O$, $R_{2a} = R_{3a} = H$; or $t = 0$;

when R is selected in group IV),

- when R_{IV} is the formula (II), $R_{IV-11} = CH_3O-$, $R_{IVd} = H$ and $R_{IVd1} = CH_3$, $X = O$ and X_1 is as above defined for Ia);
- when R_{IV} is formula (X), $R_{IVd} = H$, $R_{IVd1} = CH_3$, $X = O$ and X_1 is as above defined for Ia);
- when R_{IV} is formula (III), R_{IV-111} is



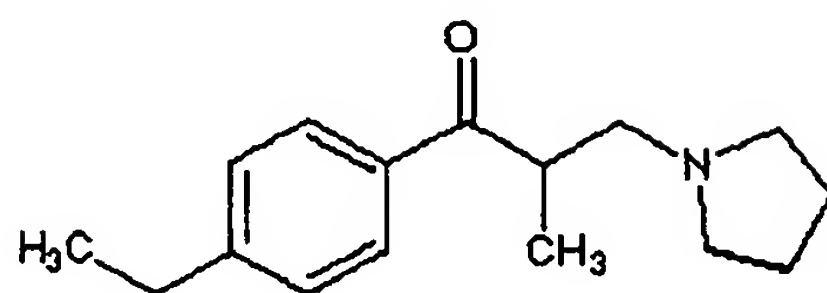
and $R_{IVd} = H$, R_{IVd1} is CH_3 , $X = O$ and X_1 is as above defined for Ia);

when R is selected in group V,

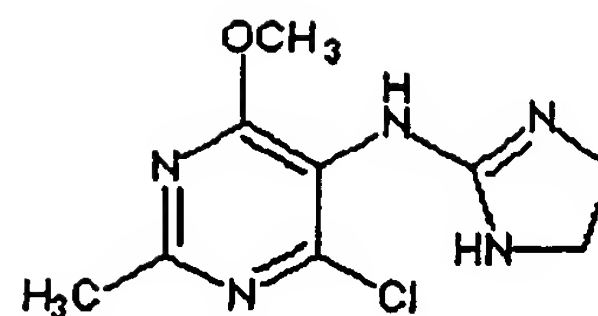
- when R is formula (II), R_{V11} and R_{V11-1} are H , and $A = R$;
- when R is formula (X), $A = RCO$, $t = 1$ and $u = 0$;
- when R is formula (XI), $A = RCO$, $t = 1$ and $u = 0$;
- when R is formula (XIII), $A = RCO$, $t = 1$ and $u = 0$;
- when R corresponds to formula (XXXX) or (XXXXI), $A = RCO$, $t = 1$ and $u = 0$.

6. Use according to claims 1-5, wherein the drugs of the nitrate salts compounds B') are selected from B'1) anticholinergic drugs, B'2) calcium antagonist drugs, B'3) drugs which facilitate the opening of the potassium channels, B'4) alpha-adrenergic agonist drugs, B'5) alpha-adrenergic antagonist drugs, B'6) beta-adrenergic agonist drugs, B'7) antidepressant drugs, B'8) GABA agonist drugs, B'9) agonist drugs of the muscarinic receptor and B'10) other drugs selected from inaperizone (B'10b), moxonidine (B'10c), papaverine (B'10e),

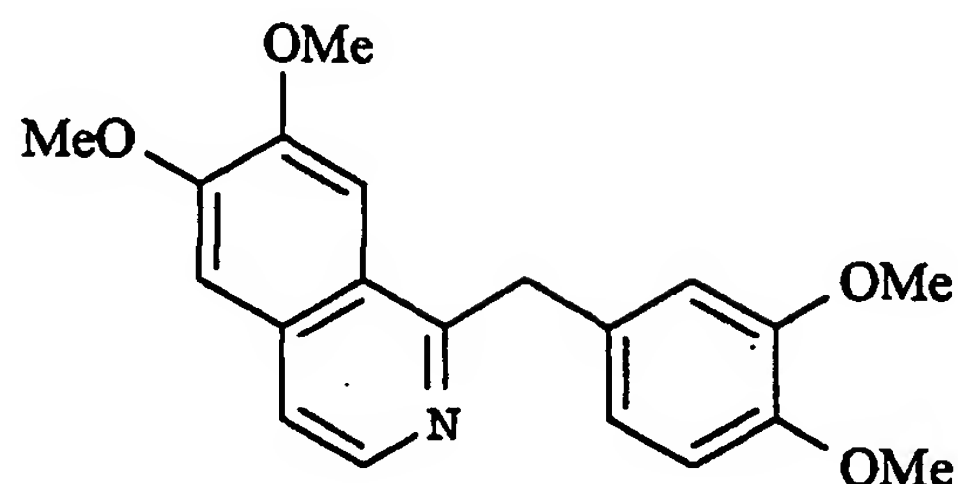
benzylamine (B'10g)



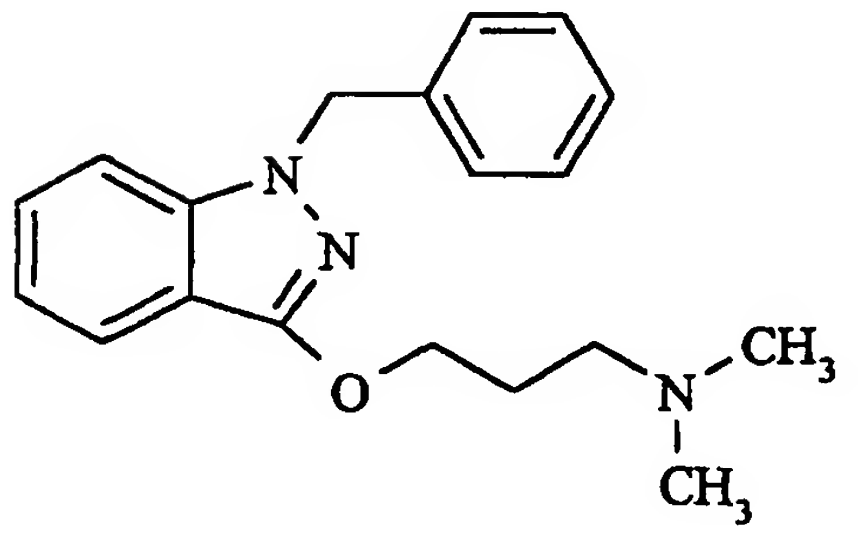
(B'10b)



(B'10c)



(B'10e)



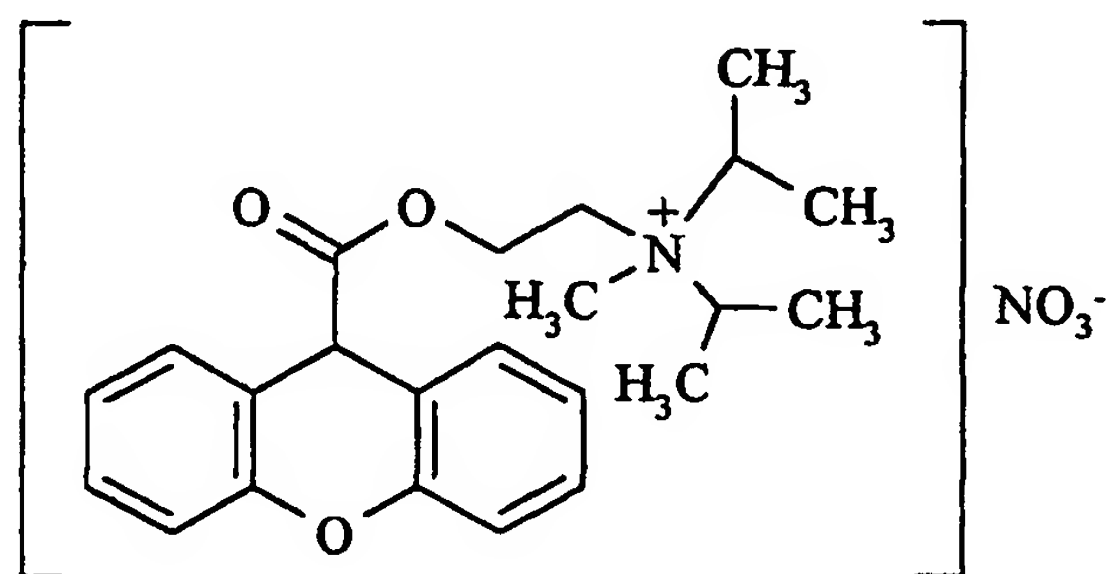
(B'10g)

B11) antagonist serotonergic drugs of the 5-HT₄ receptor.

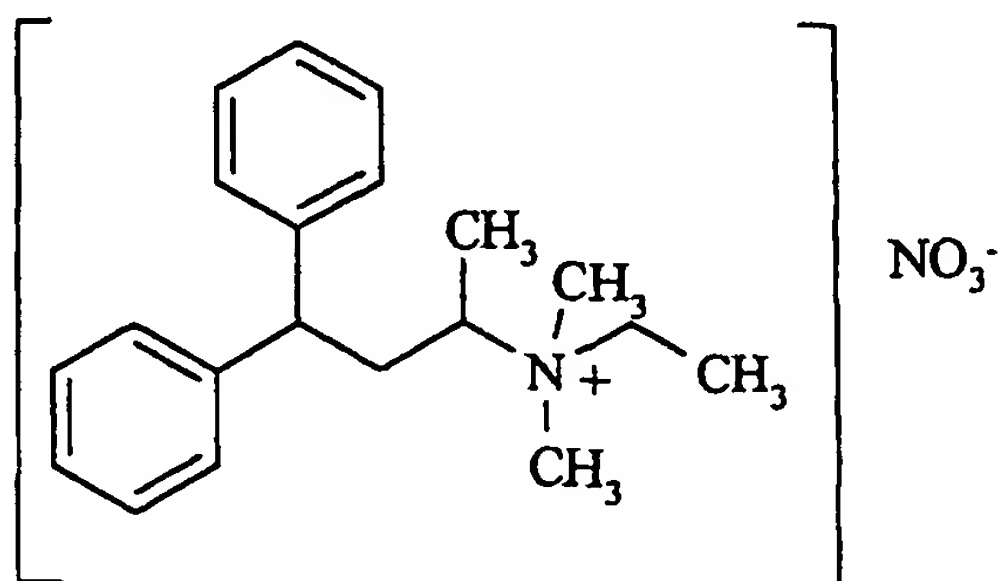
7. Use according to claim 6, wherein the compounds B') are selected from the following:

B'1) propantheline (B'1a), emepronium (B'1b), trospium (B'1c), tolterodine (B'1d), darifenacin (B'1e), vamicamide (B'1f), zamifenacin (B'1g), atropine (B'1h), cycloclrine (B'1i), oxybutynin (B'1l), N-desethyl-oxybutynin (B'1l-I), dicyclomine (B'1m),

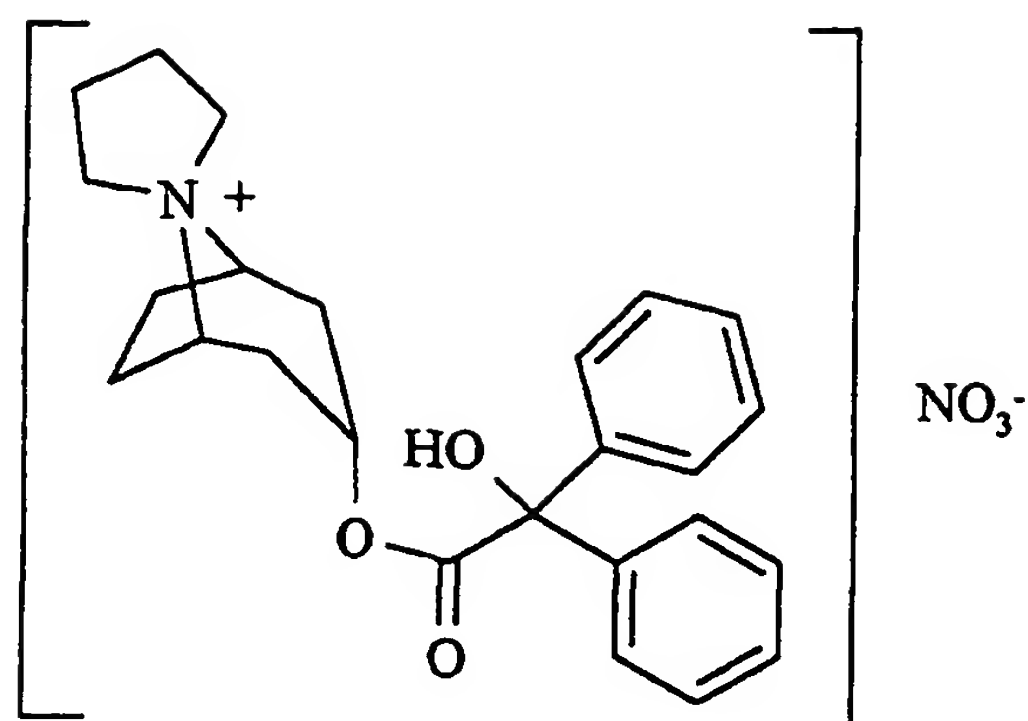
- propiverine (B'1n), flavoxate (B'1o), terodiline (B'1p);
- B'2) nifedipine (B'2a), flunarizine (B'2b), diltiazem (B'2c);
- B'3) pinacidil;
- B'4) ephedrine (B'4a), pseudoephedrine, phenylpropanolamine (B'4c), midodrine (B'4d), de-glymidodrine (B'4e);
- B'5) alfuzosin (B'5a), doxazosin (B'5b), prazosin (B'5c)
- B'6) clenbuterol (B'6a), terbutaline (B'6b), formoterol (B'6c);
- B'7) imipramine (B'7a), clozapine (B'7b), milnacipran (B'7c), fluphenazine (B'7d), nortriptyline (B'7e), duloxetine (B'7f);
- B'8) baclofen;
- B'9) bethanechol;



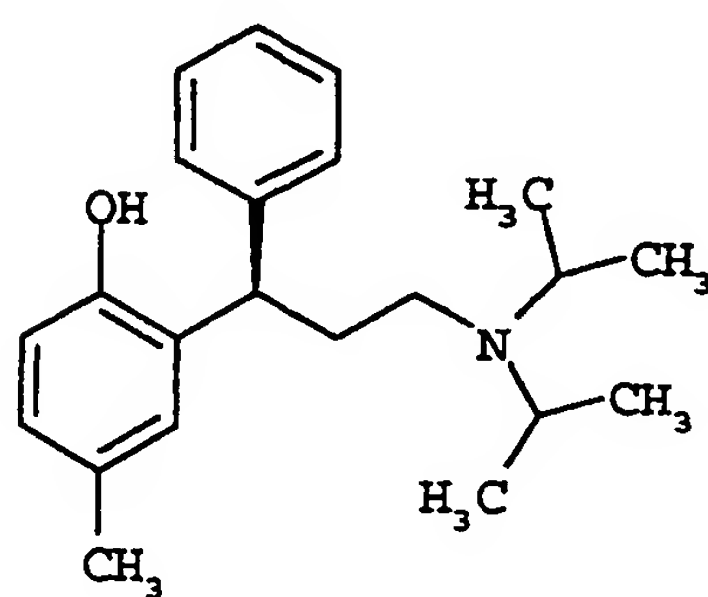
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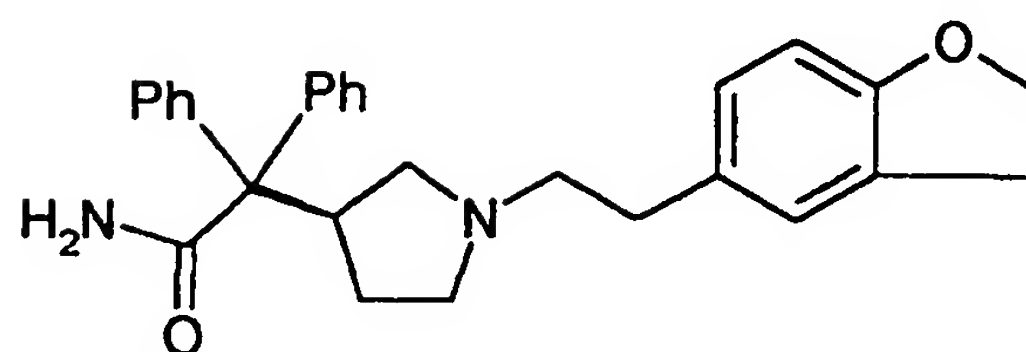
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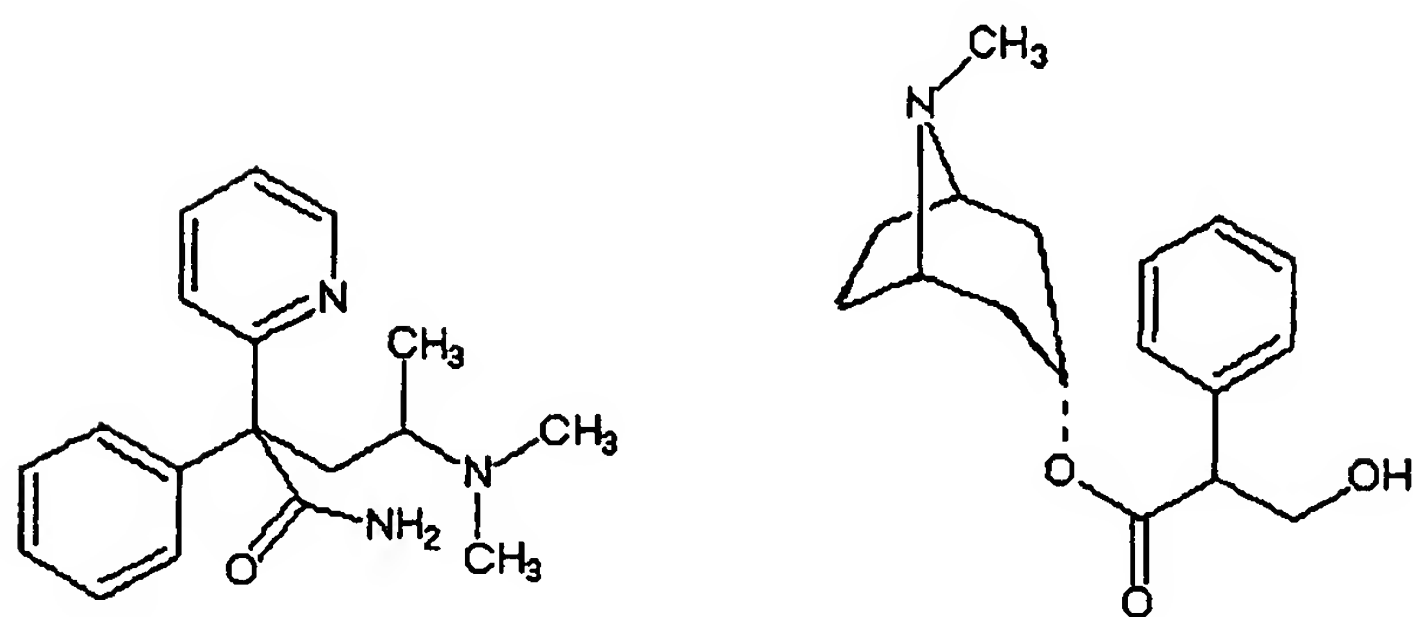
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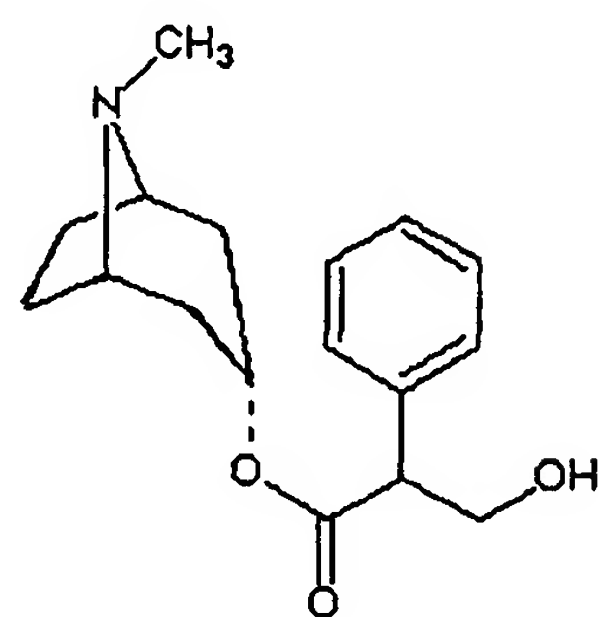
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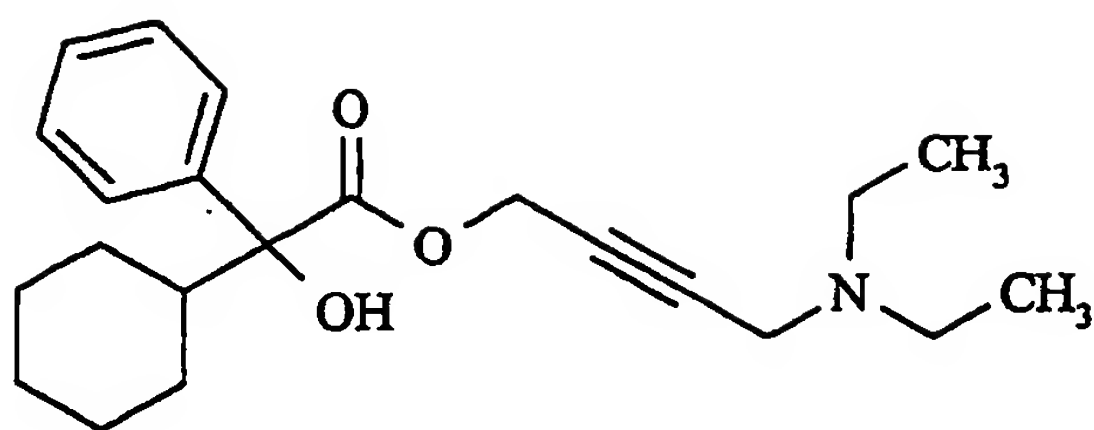
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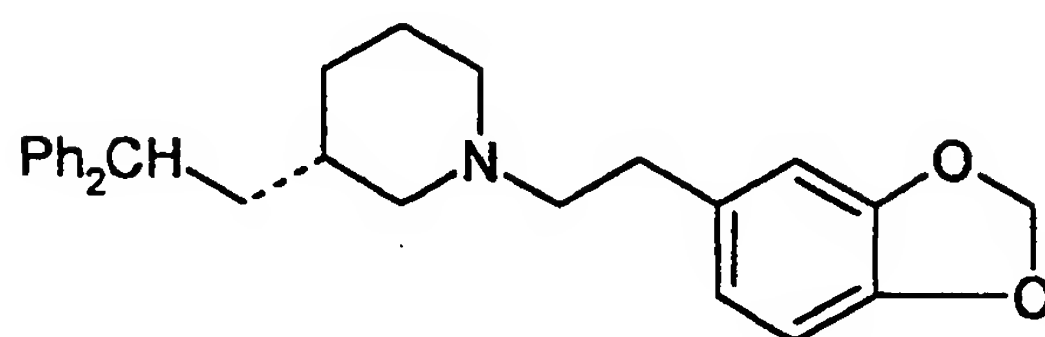
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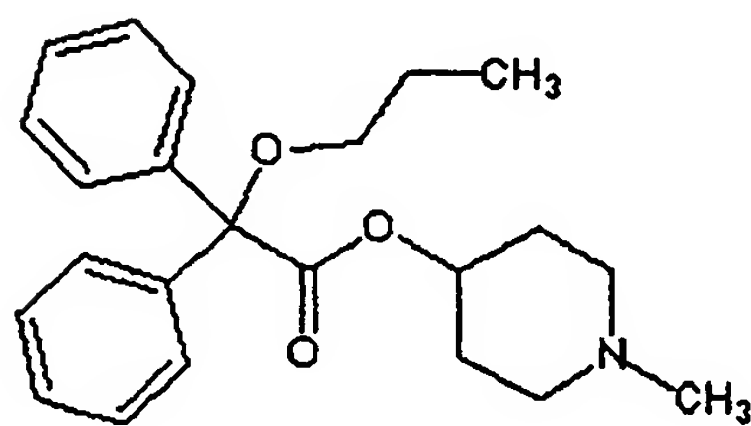
(B'1h)



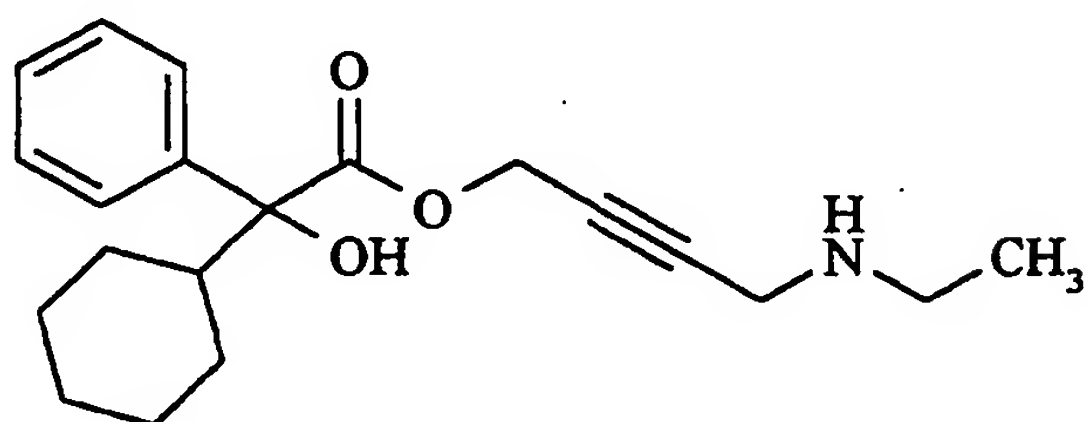
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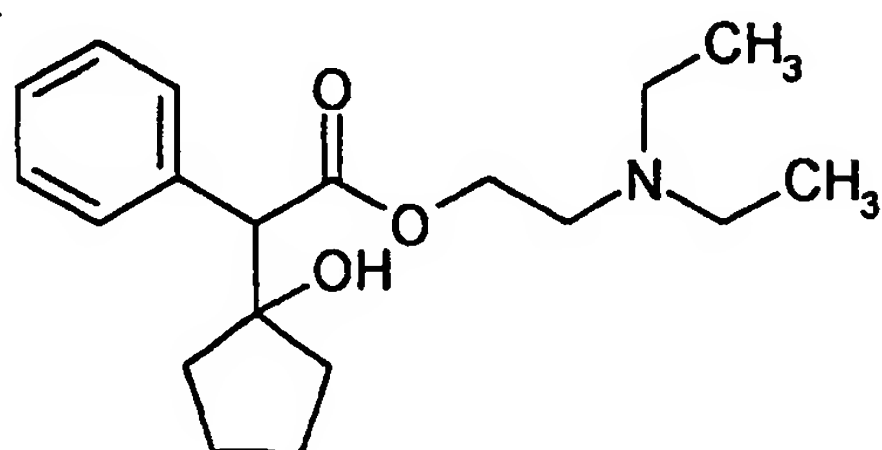
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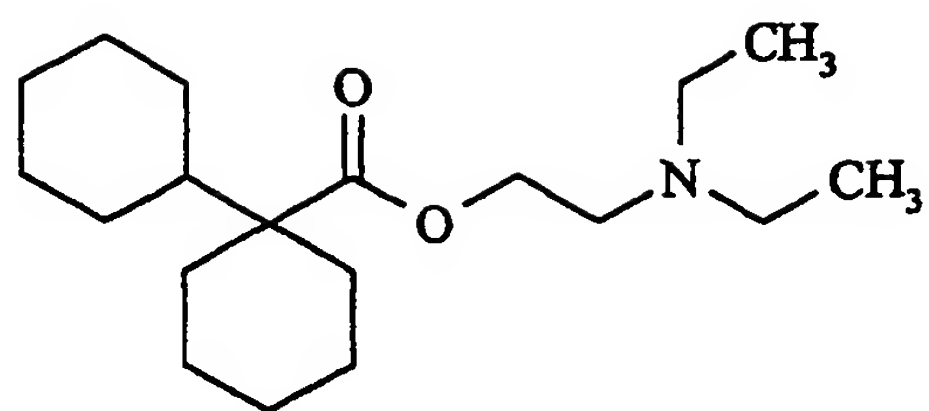
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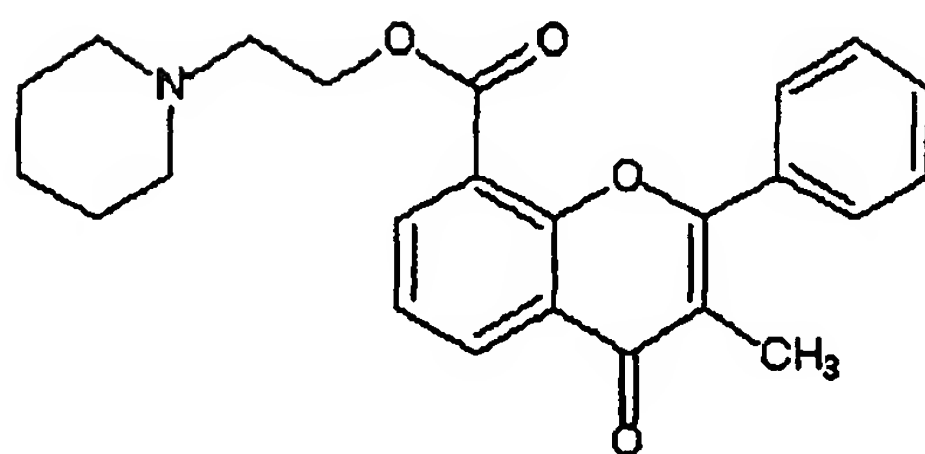
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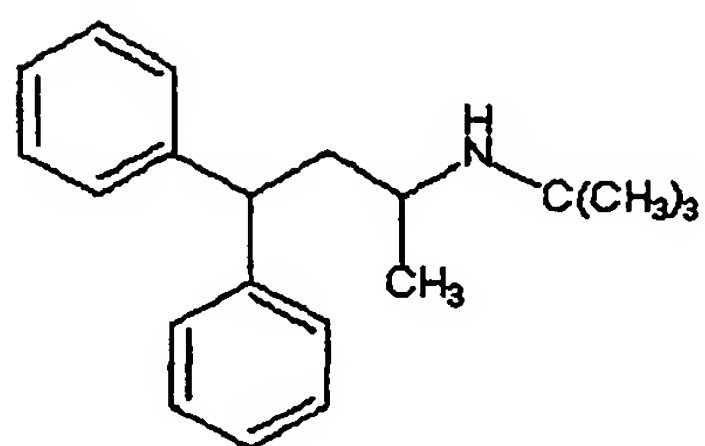
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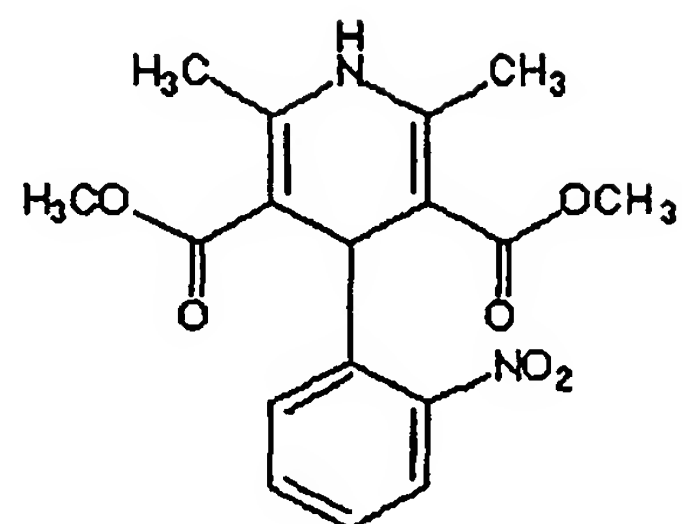
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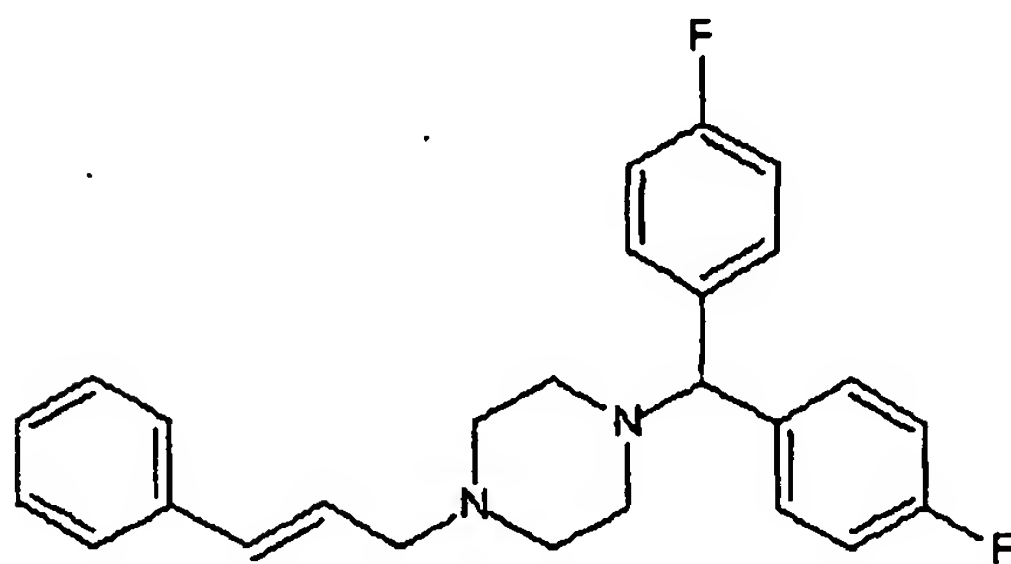
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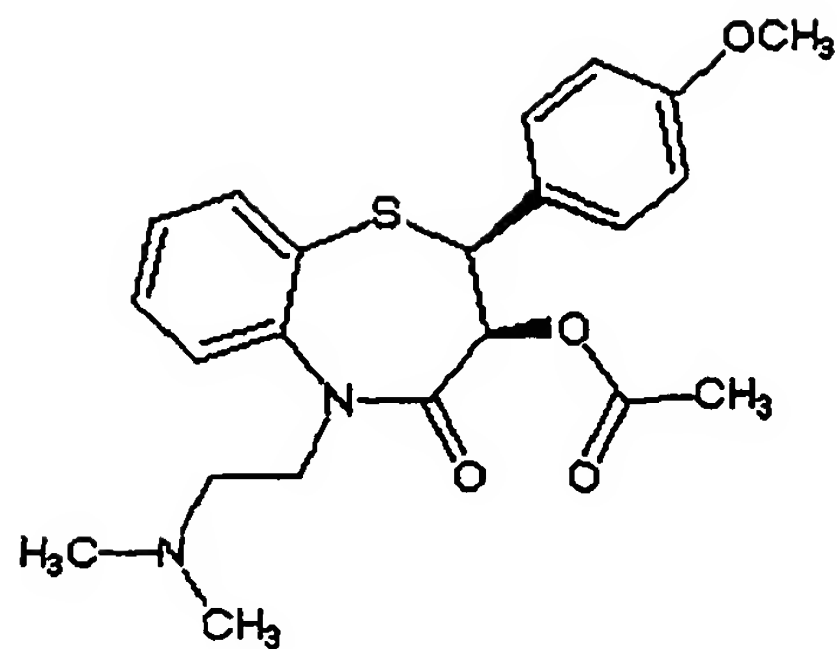
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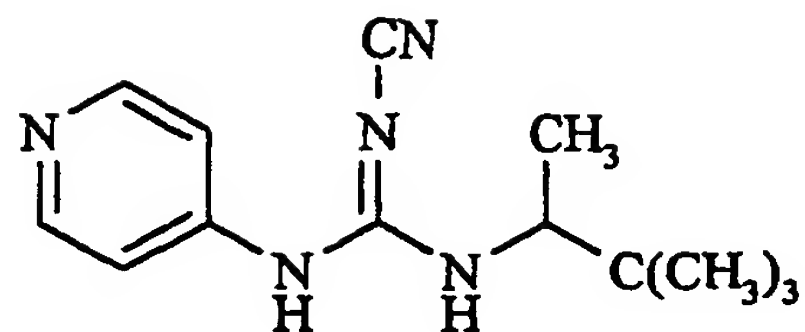
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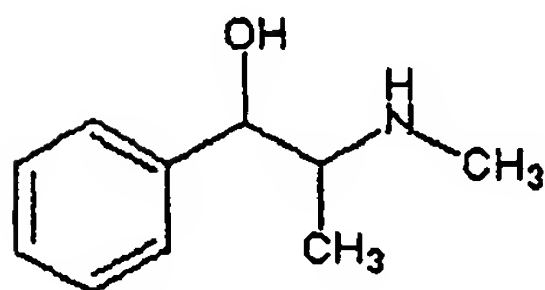
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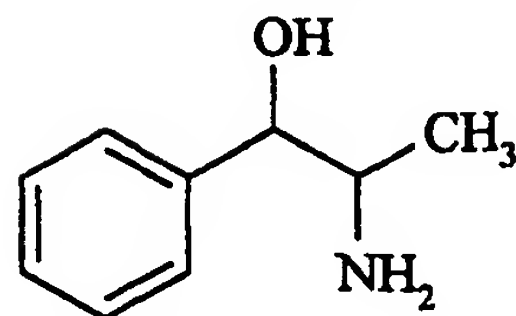
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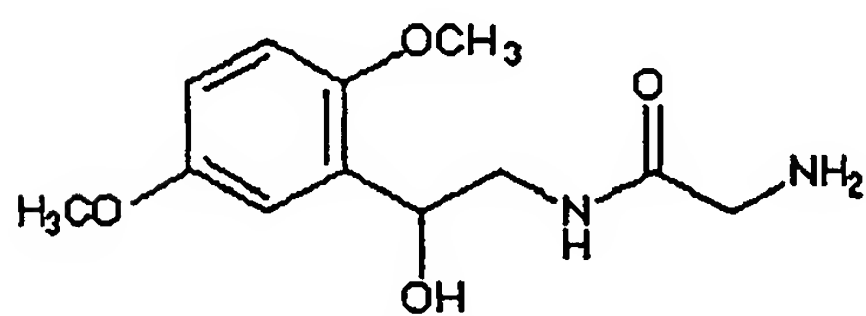
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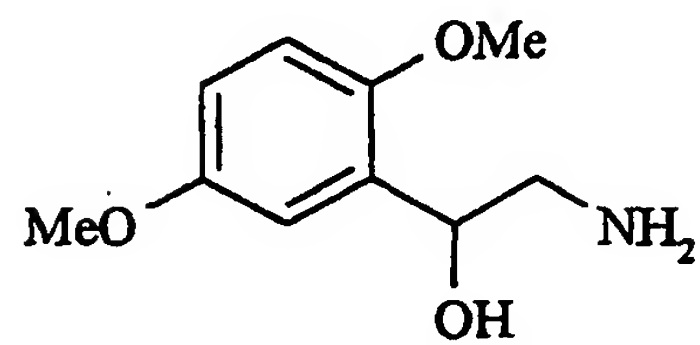
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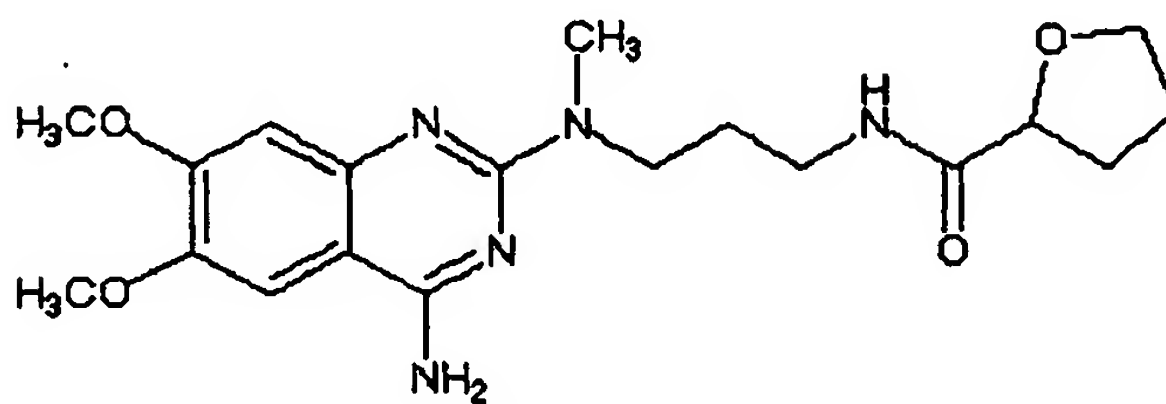
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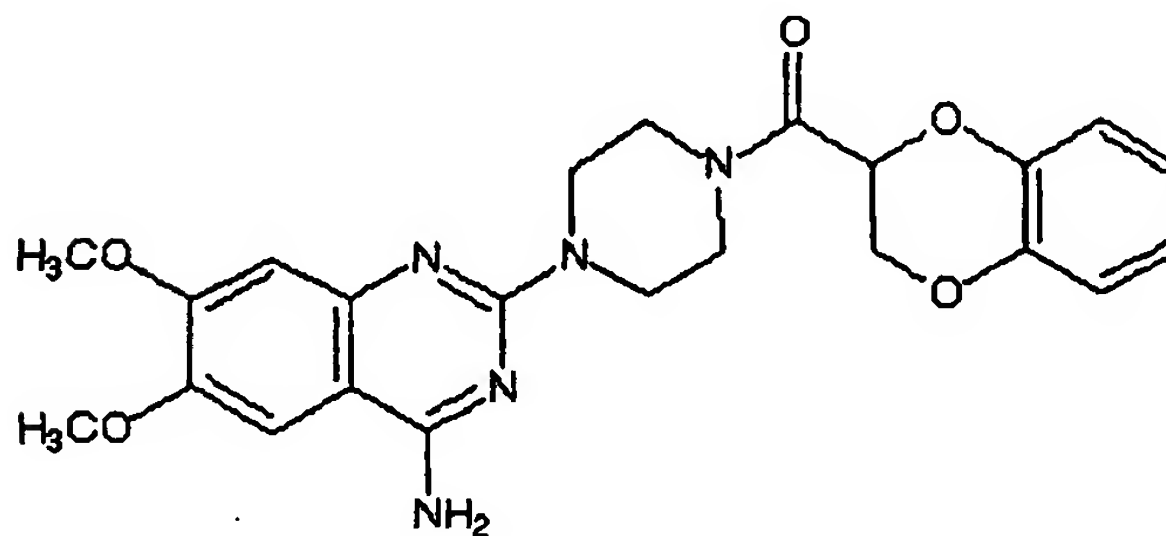
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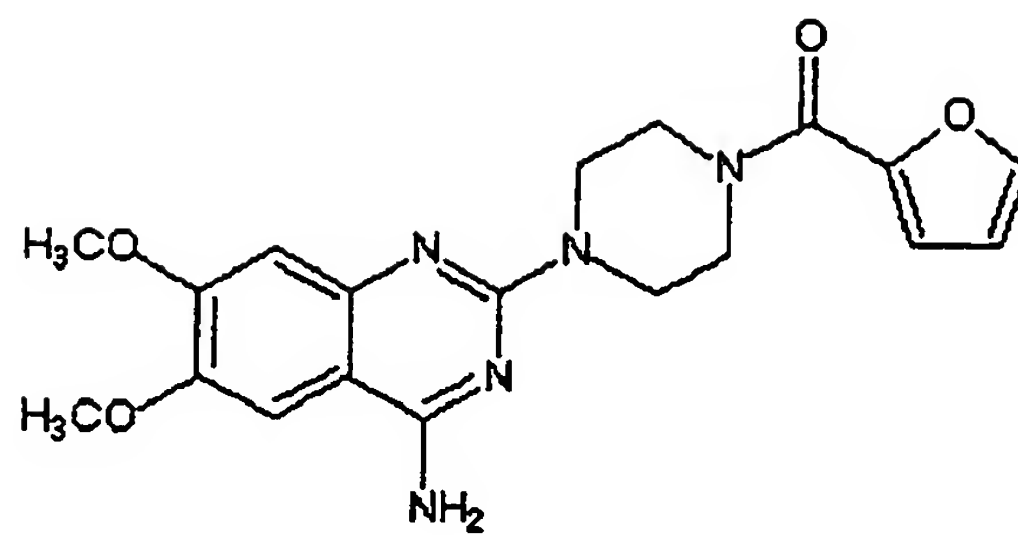
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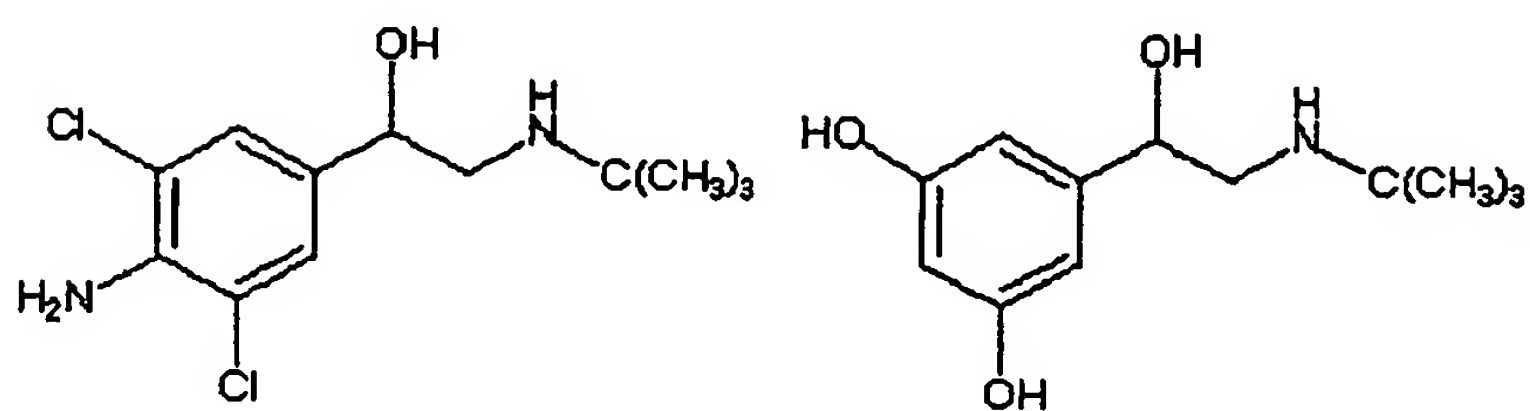
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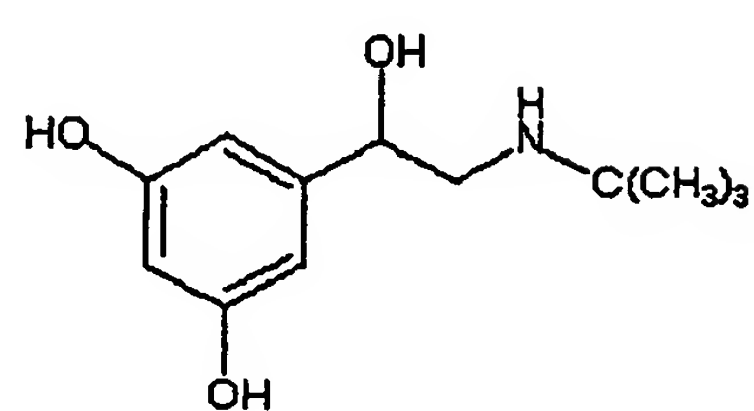
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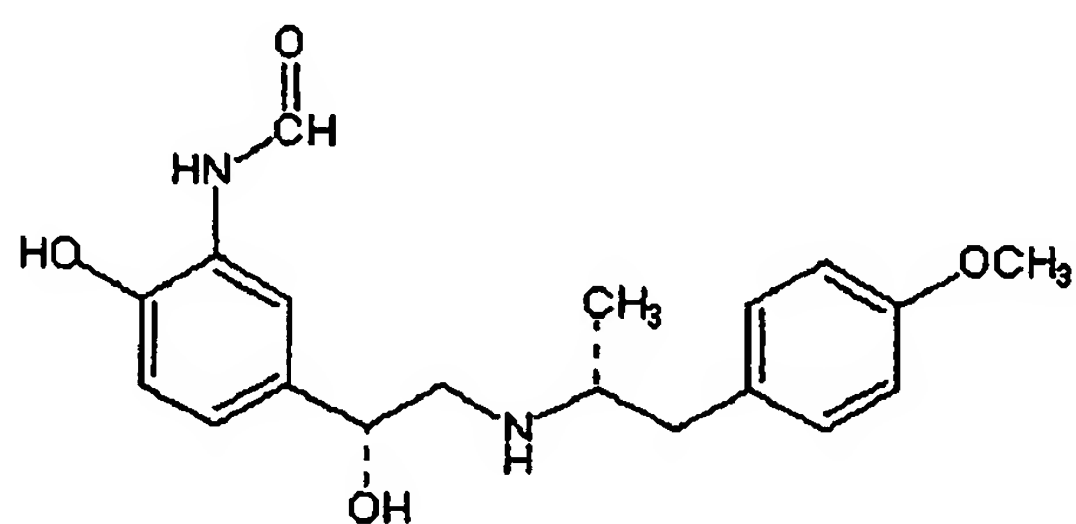
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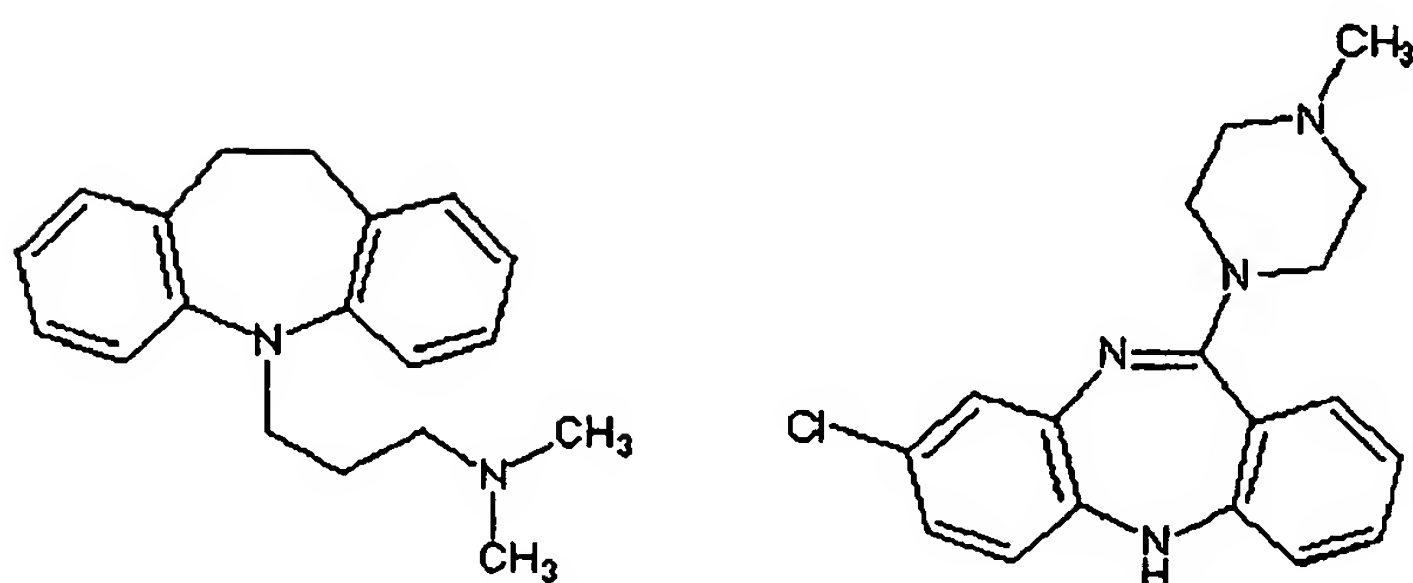
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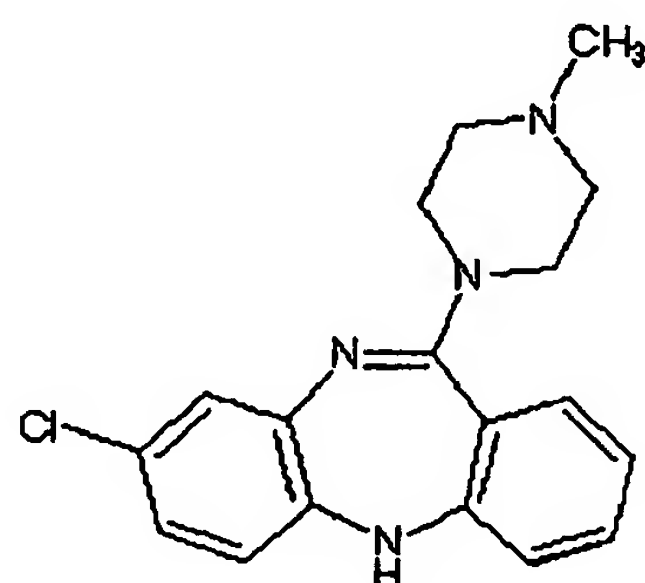
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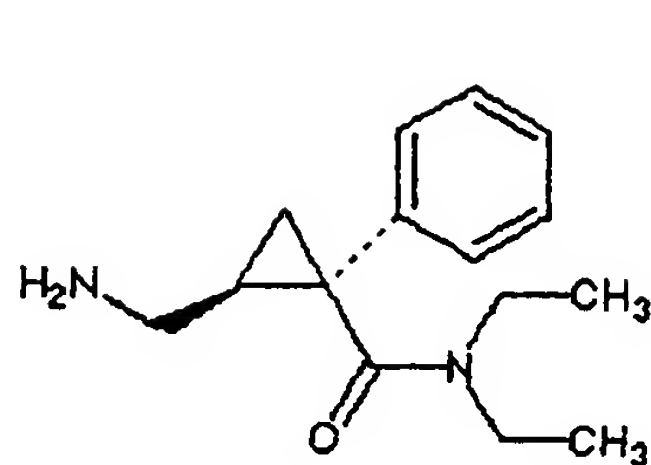
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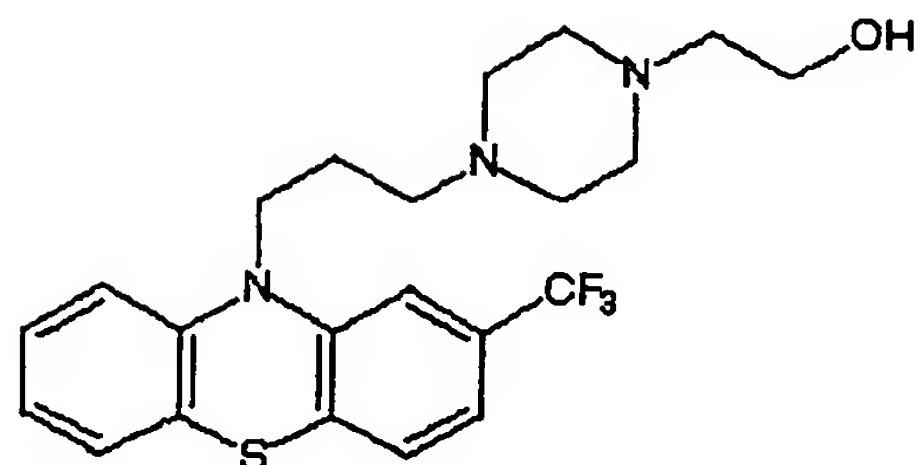
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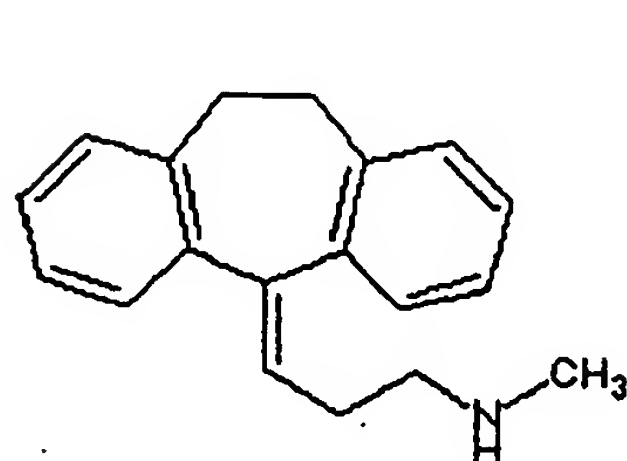
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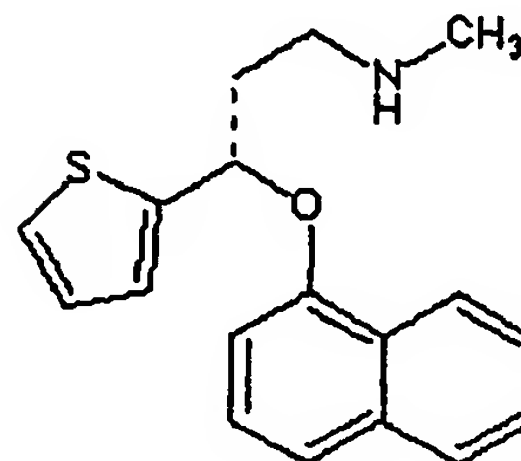
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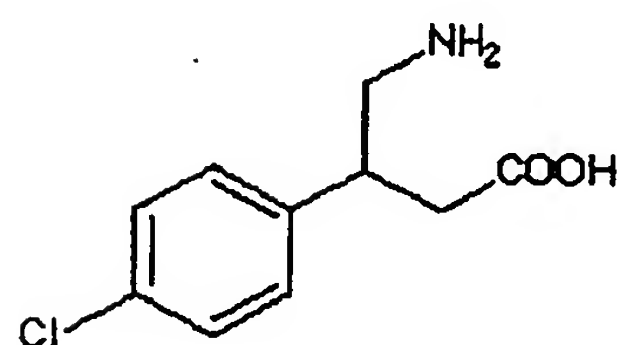
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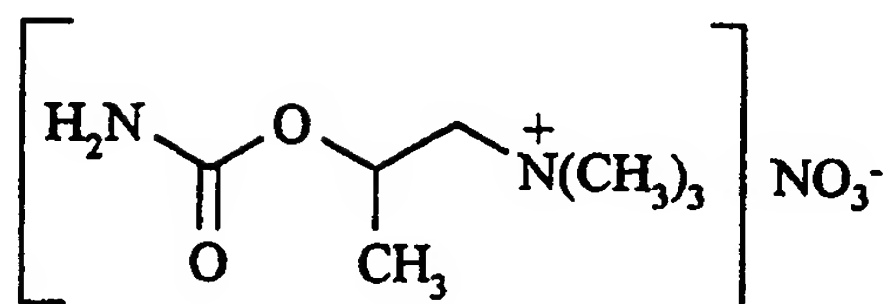
(B'7e)



(B'7f)



(B'8)



(B'9)

B'11) 3-(piperidin-1-yl)propyl 4 amino-5-chloro-2-methoxy benzoate (B'11a), 1-[4-amino-5-chloro-2-(3,5-dimethoxy phenyl)methyl oxy]-3-[1-[2-methylsulphonylamino]ethyl piperidin-4-yl]-1-propanone (B'11b) 1-piperidinylethyl-1H-indol-3-carboxylate (B'11c), (S)-2-chloro-5-methoxy-4-[5-(2-piperidylmethyl)-1,2,4-oxadiazol-3-yl] aniline (B'11d).

8. Use according to claims 1-7, wherein the compounds inhibiting the phosphodiesterase C) salifiable with organic or inorganic acids are selected from the following: (C1) 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazol[4,3-d]-pyrimidin-5-yl)-phenyl]sulphoyl]-4-methyl-piperazine (Sildenafil), (C2) 2-(2-propyloxyphenyl)-8-azapurin-6-one (Zaprinast), (C3) 2,6-bis-(diethanolamino)-4,8-dipiperidino pyrimido [5,4-d]-pyrimidine (dipyridamol), (C4) 6-chloro-4-(1,3-dioxain-

dan-5-yl)methylamino-2(4-carboxy-1-piperidinyl)-quinazoline, (C5) N-(phenylmethyl)-1-ethyl-1H-pyrazol-[3,4-b]-quinolin-4-amine, (C6) 1-(2-chlorobenzyl)-3-isobutyryl-2-propyl-6-aminocarbonyl-indol, (C7) 1-benzyl-6-chloro-2-[1-[3-(imidazol-1-yl)propyl]indol-5-yl-amino carbonyl]benzimidazol, (C8) 2-(1-imidazolyl)-5-(phenyl)-4-(1,3-dioxaindan-5-yl)methyl aminopyrimidine, (C9) 6-ethynyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl) quinazoline, (C10) 1-cyclopentyl-3-ethyl-6-(2-propoxy-phenyl)pyrazol[3,4-d]pyrimidin-4-one, (C11) 1-cyclopentyl-3-ethyl-6-(4-methoxybenzyl)-pyrazol-[3,4-d]-pyrimidin-4-one, (C12) 1,3-dimethyl-6-(2-propoxy-5-methansulphonamidophenyl)-1,5-dihydro pyrazol[3,4-d]-pyrimidin-4-one, (C13) (6R, 12aR)-2,3, 6,7,12, 12a-hexahydro-2-methyl-6-(1,3-dioxan-5-yl)pyrazino [2',1':6,1] pyri-do[3,4-b]indol-1,4-dione, (C14) 1-propyl-3-methyl-6-[2-propoxy-5-[(4'-methyl-1-pyrazinyl) sulphonamido] phenyl]-1,5-dihydropyrazol[3,4-d]pyrimidin-4-one, (C15) 3-(4-amino carbonyl-1-piperidinyl)-6-cyan-8-(3-chloro-4-methoxy-phthalazine, (C16) 2-(1-imidazolyl)-4-(1,3-dioxaindan-5-yl) methylamino-7,8-dihydro-5H-thiopyran[3,2-d]pyrimidine (C17) 1-Cyclopentyl-3-ethyl-6-(3-ethoxypyrid-4-yl)-1H-pyrazolo[3,4-d] pyrimidin-4-one, (C18) 1-[3-[1-[(4-Fluorophenyl)methyl]-7,8-dihydro-8-oxo-1H-imidazo[4,5-g]quinazolin-6-yl]-4-propoxyphenyl] carboxamide.

9. Use according to claim 8, wherein the organic salts of C) are selected from oxalate, tartrate, maleate, succinate, citrate, glycinate, lysinate; and the inorganic anions are selected from nitrate, chloride, sulphate, phosphate.
10. Use according to claims 8-9, wherein the preferred anion is nitrate.
11. Use according to claims 1-10, obtained with formulations by oral, parenteral use containing one or more salts of the drugs of classes A)-C).
12. Nitrate salts of drugs compounds B') of claims 1, 6 and 7, excluding the nitrate salts respectively of nifedipine, flunarizine, diltiazem.
13. Nitrate salts of drugs compounds C) of claims 1, 8 and 9 excluding sildenafil nitrate, zaprinast nitrate and dipyridamol nitrate.

14. Formulations according to claim 11.
15. Nitrate salts according to claims 12-13 for use as a medicament.

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(54) Title: **DRUGS FOR SEX DYSFUNCTIONS**

(57) Abstract: Use in sex dysfunctions of one or more of the following classes of drugs selected from the following: B) Salified and not salified, nitric oxide-donor drugs, of formula A-X₁-N(O)_z, C) Organic or inorganic salts of compounds inhibiting phosphodiesterases.

WO 02/11706 A2

DRUGS FOR SEX DYSFUNCTIONS

* * * * *

The present invention relates to drugs to be utilized for systemic and topical use in the sex dysfunction therapy, specifically in the male impotence and in female sex dysfunctions.

All over the world there is a progressive ageing of the population. It is expected that in about 5 years 17% of the population is over sixty-five. This phenomenon involves important consequences not only from a sociological point of view, but also from an epidemiological point of view. If at the beginning of the century the diseases having a greater impact on mortality and morbidity were the infectious ones, now other kinds of diseases have a greater importance. Among these, sex dysfunctions in both sexes are to be considered, which affect a very significant percentage of the population, especially due to the progressive ageing.

The male impotence or erectile dysfunction is a diffused disease. In the United States it is estimated that the impotence regards from 10 to 20 millions people over 18 years and that in the male population over forty the impotence reaches a percentage of 52%. Analogously, also a very high percentage of women (up to 76%) suffers from sex dysfunctions. For both pathologies sildenafil citrate is commonly used even though with not completely satisfactory results. The sildenafil citrate is an active drug by os exerting a beneficial vasoactive action in the male sex district. The main problem connected to the administration of this drug resides in the impossibility to dissociate its efficacy from the toxic effects, since sildenafil citrate acts strengthening the effects induced by a high production of nitric oxide, (J. Urol. 1998, 160, 257-61) and under these conditions it causes significant toxic effects. Indeed the drug is badly tolerated in patients subjected to therapy with nitrate drugs and it causes cephalaea in more than 16% of the cases, so that the use is contraindicated in these therapeutic treatments. The drug is badly tolerated even when it is taken by patients affected by pathologies characterized by a high endogenous

hyperproduction of nitric oxide, such as for example cardiomyopathies (J. Am. Coll. Cardiol. 29, 716-24, 1997), infarct (Am. J. Hypertens. 1, 174-182 1999), cardiac decompensation. It is indeed known that the Sildenafil citrate has caused serious, even lethal, side effects in cardiopathic patients (Am. J. Cardiol. 84/5B, 11N-17N, 1999).

From the patent application WO 99/67231 the relaxing effect on the cavernous artery and on the cavernous body (vasodilator effect at a peripheric level) of the sildenafil nitrate salt and of the native sildenafil (citrate salt) is known. In the pharmacological experiment described in said application no information is given on the vascular tolerability of the compound in patients affected by various pathologies, for example cardiovascular pathologies. Indeed the vascular tolerability is a critical aspect if one considers that the medical speciality on the market which contains the sildenafil citrate salt is contraindicated, as above said, in cardiopathic patients.

The need was felt to have available drugs for sex dysfunctions not showing the aforesaid side effects of the citrate sildenafil.

The Applicant has unexpectedly and surprisingly found compounds able to solve this technical problem.

An object of the present invention is the systemic use, in particular oral and sublingual use, for the treatment of sex dysfunctions of one or more of the following classes of drugs:

- A) organic or inorganic compounds or salts thereof, having general formula:



as defined hereinunder,

- C) Nitrate salts of compounds able to inhibit phosphodiesterases;

in the compounds of general formula:

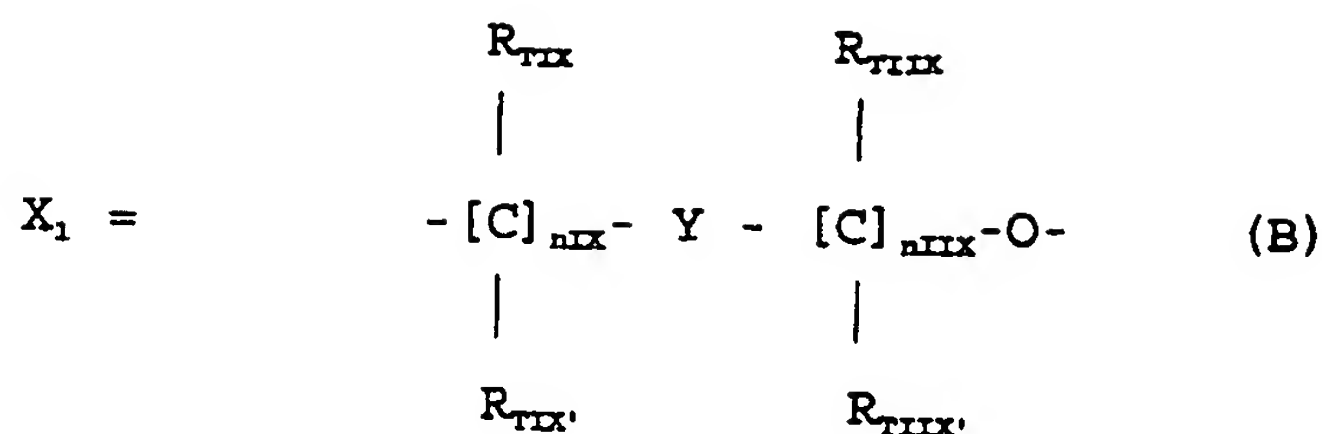


z is an integer and it is 1 or 2, preferably 2;

A = $R(COX_u)_t$ and wherein t is an integer 0 or 1; u is 0 or 1;

X = O, NH, NR_{10} , wherein R_{10} is a linear or branched C_1 - C_{10} alkyl;

X_1 is the following bivalent linking group:



wherein:

nIX is an integer in the range 0-3, preferably 1;

$nIIX$ is an integer in the range 1-3, preferably 1;

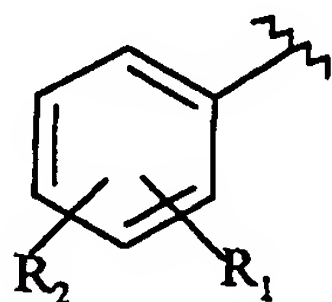
R_{TIX} , $R_{TIX'}$, R_{TIIIX} , $R_{TIIIX'}$, equal to or different from each other are H or linear or branched C_1 - C_4 alkyl; preferably R_{TIX} , $R_{TIX'}$, R_{TIIIX} , $R_{TIIIX'}$ are H;

Y is a heterocyclic ring containing one or two nitrogen atoms, optionally one oxygen or sulphur atom, said saturated, unsaturated or aromatic ring, having 5 or 6 atoms.

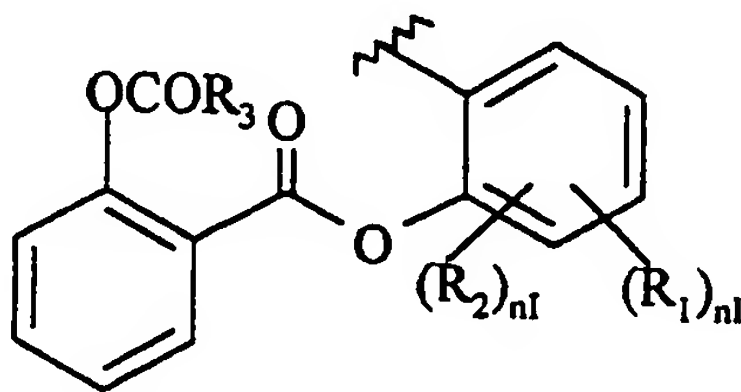
R is selected from the following groups:

Group I) wherein $t = 1$ and $u = 1$

Ia)



Ib)



wherein:

R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or linear or branched C_3 - C_5 alkyl, or the residue of a heterocycle with only one ring having 5 or 6 atoms which can be aromatic, partially or totally hydrogenated, containing one or more heteroatoms independently selected from O, N and S;

R_2 is hydrogen, hydroxy, halogen, linear or branched when possible C_1 - C_4 alkyl; a linear or branched when possible C_1 - C_4 alkoxy; a linear or branched when possible C_1 - C_4

perfluoroalkyl, for example trifluoromethyl; nitro, amino, mono- or di-(C₁₋₄) alkylamino;

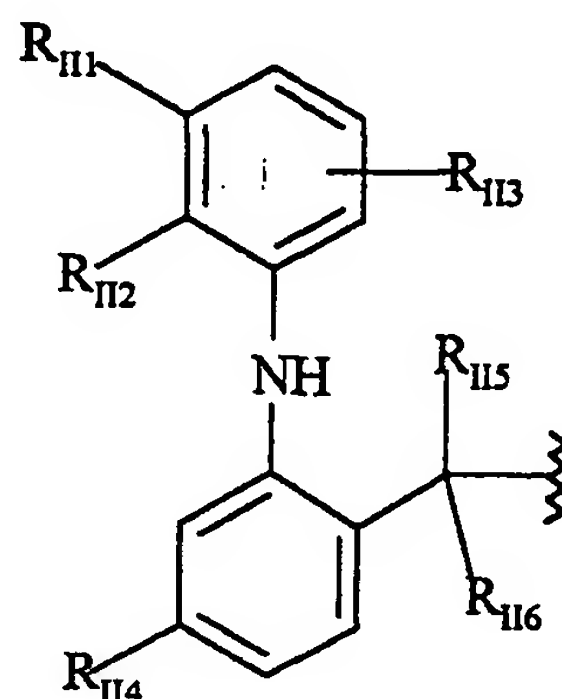
nI is an integer 0 or 1;

preferably in the compounds of formula Ia) X is equal to O or NH, R₁ is acetoxy, preferably in ortho position with respect to -CO-, R₂ is hydrogen; preferably X₁ is the linking group (B) wherein R_{TX} = R_{TX} = R_{TX} = R_{TX} = H, n_{TX} = n_{TX} = 1;

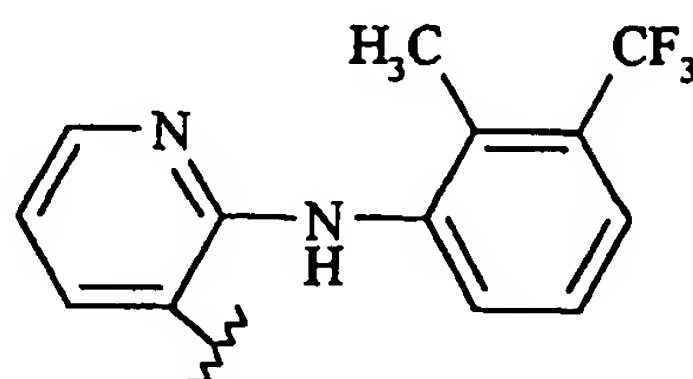
Preferably in the compounds of formula Ib) R₃ = CH₃, nI = 0, X is equal to O, X₁ is as above defined for Ia); in this case Ib) is the residue of the acetylsalicylsalicylic acid;

Group II, wherein t = 1, u = 1

IIa)



IIb)



wherein:

R_{II5} is H, linear or branched when possible C₁-C₃ alkyl;

R_{II6} has the same meaning as R_{II5}, or when R_{II5} is H it can be benzyl;

R_{II1}, R_{II2} and R_{II3} can independently be hydrogen, linear or branched when possible C₁-C₆ alkyl, or linear or branched when possible C₁-C₆ alkoxy, or Cl, F, Br;

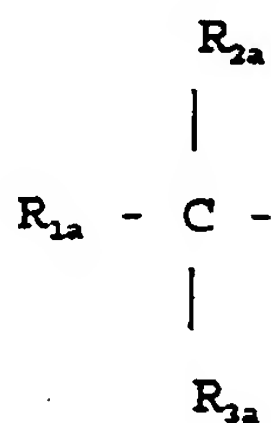
R_{II4} is R_{II1} or bromine;

the compounds wherein R_{II1}, R_{II4} are hydrogen and R_{II2} and R_{II3} are chlorine in ortho position with respect to NH are preferred;

R_{115} and R_{116} are H, X is equal to O, and X_1 is as above defined for the compounds of formula Ia);

I Ib) is the residue of the 2-[(2-methyl-3-(trifluoromethyl)phenyl]amino]-3-pyridincarboxylic acid and when the -COOH group is present the compound is known as flunixin;

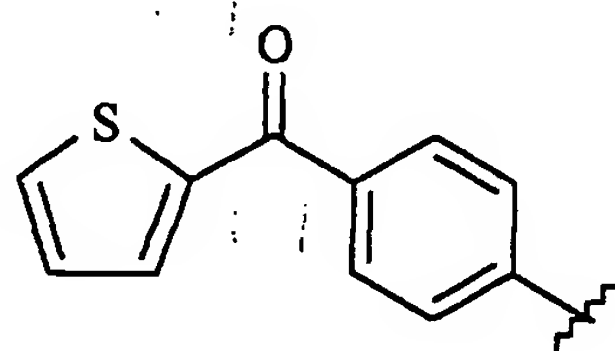
Group III) wherein $t = 1$, $u = 1$ and R is



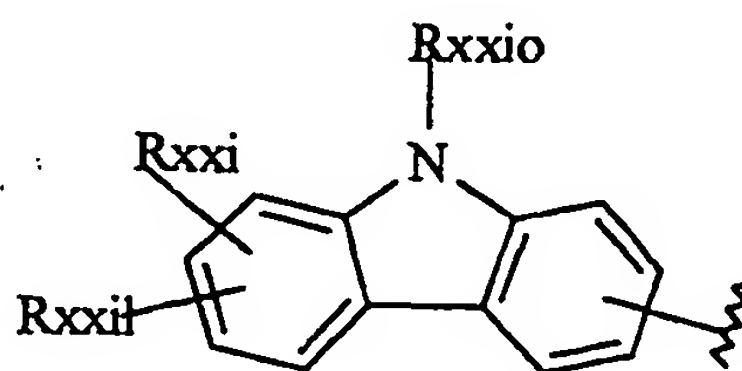
wherein:

R_{2a} and R_{3a} are H, linear or branched when possible, substituted or not, C_1 - C_{12} alkyl or allyl, with the proviso that if one of the two is allyl, the other is H; preferably R_{2a} is H, C_1 - C_4 alkyl, R_{3a} is H;

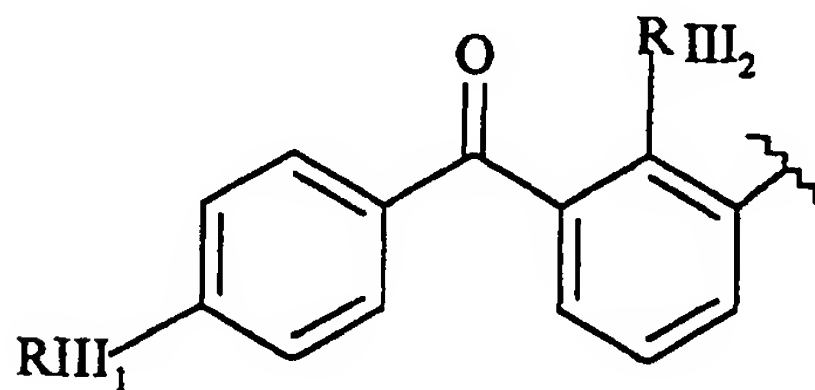
R_{1a} is selected from



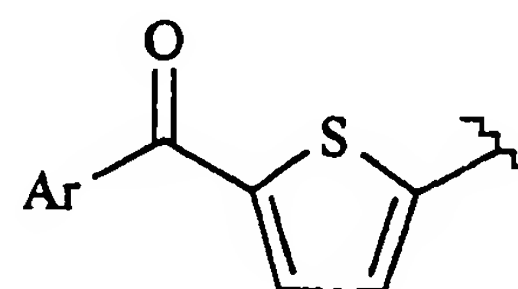
(II)



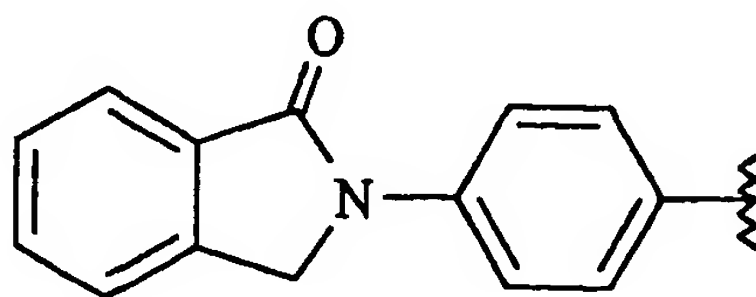
(XXI)



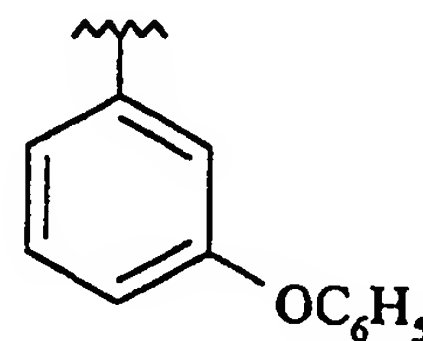
(IV)



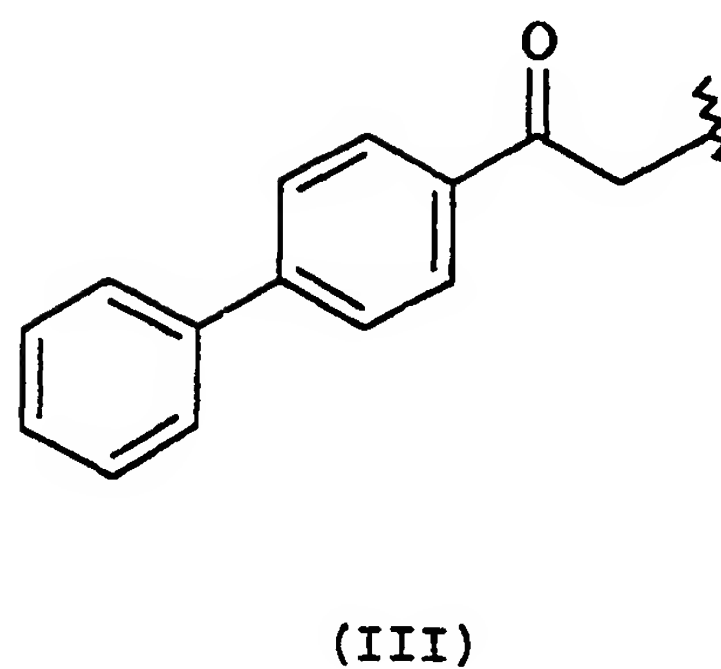
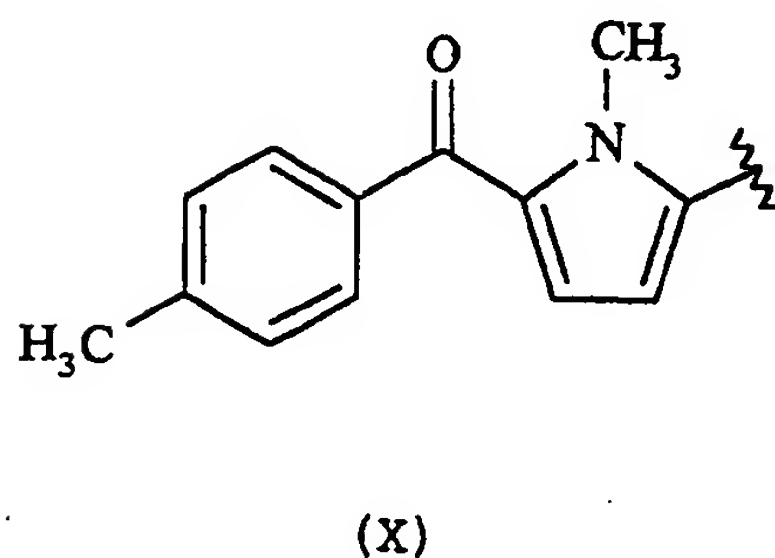
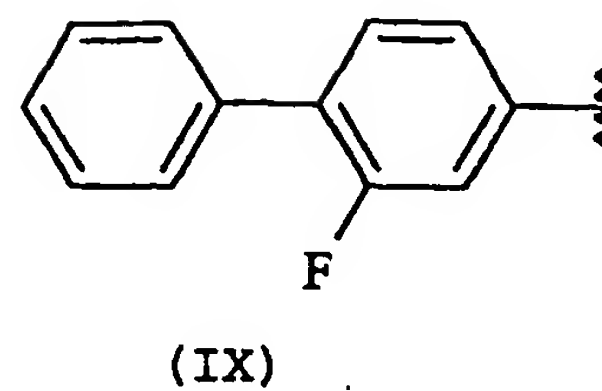
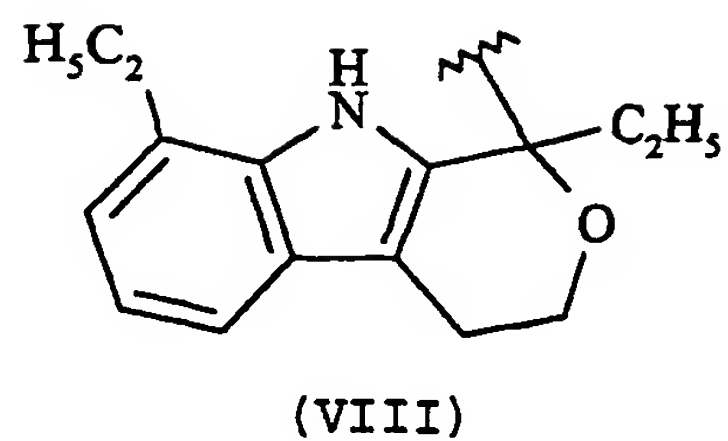
(XXXV)



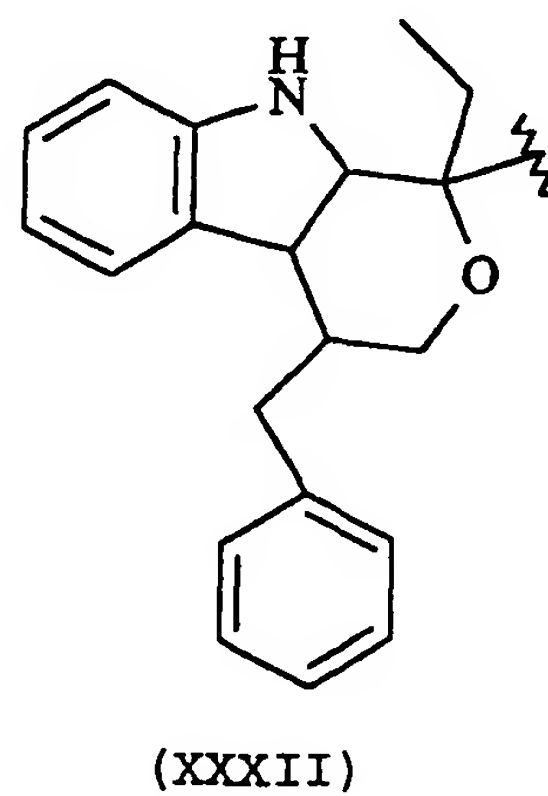
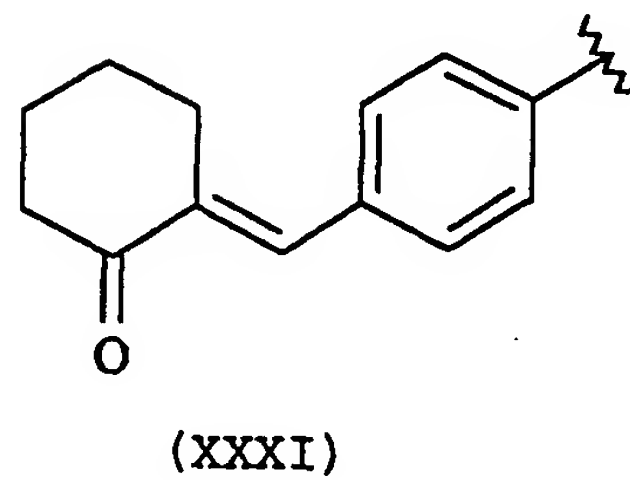
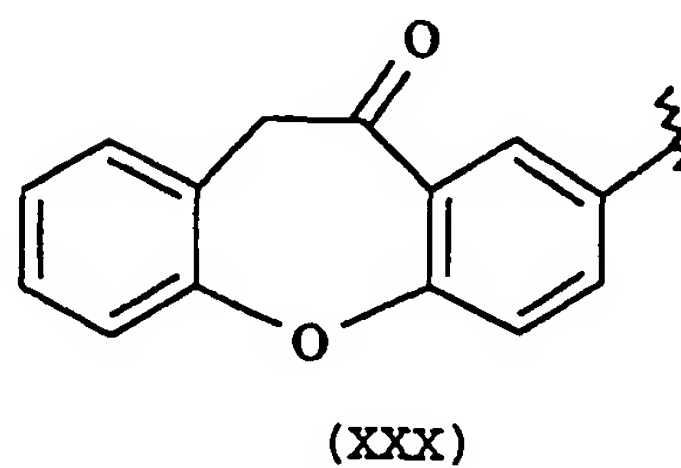
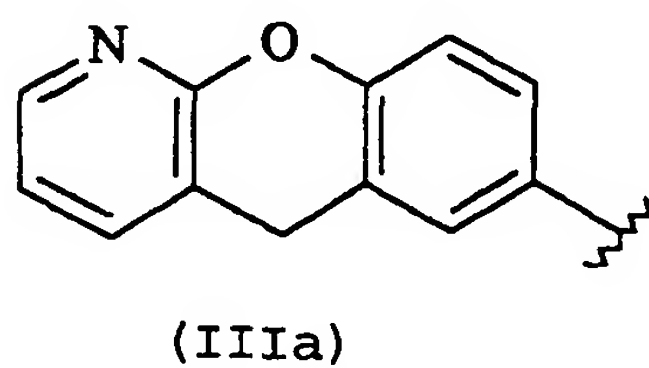
(VI)

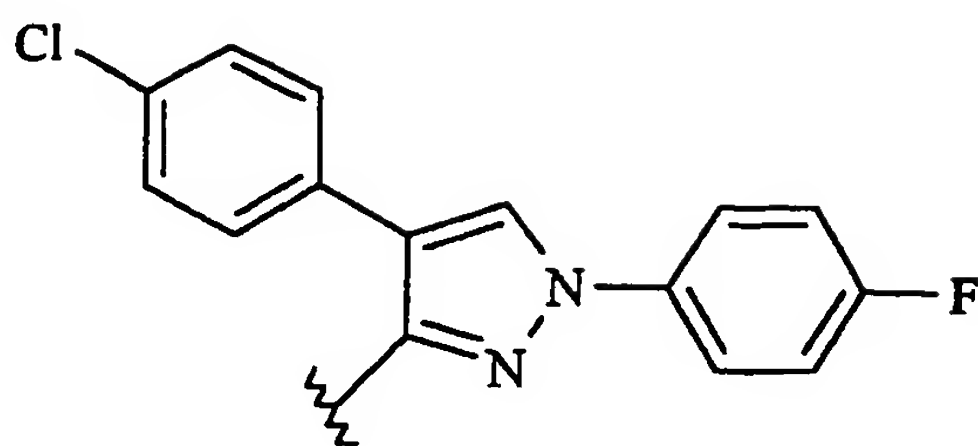


(VII)

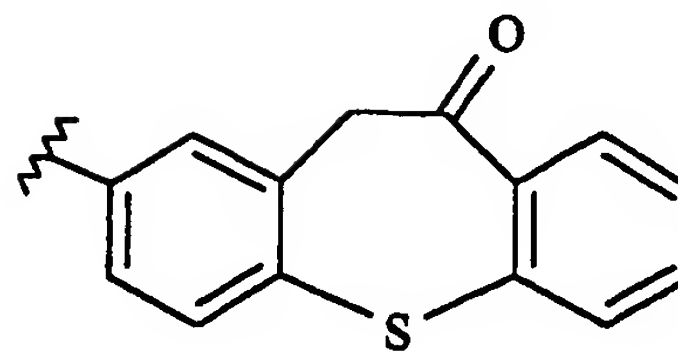


IIID) R_{1a} corresponds to the following formulas:

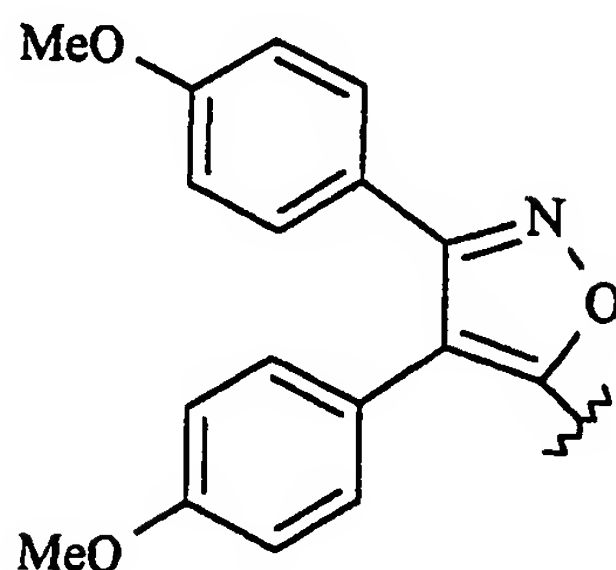




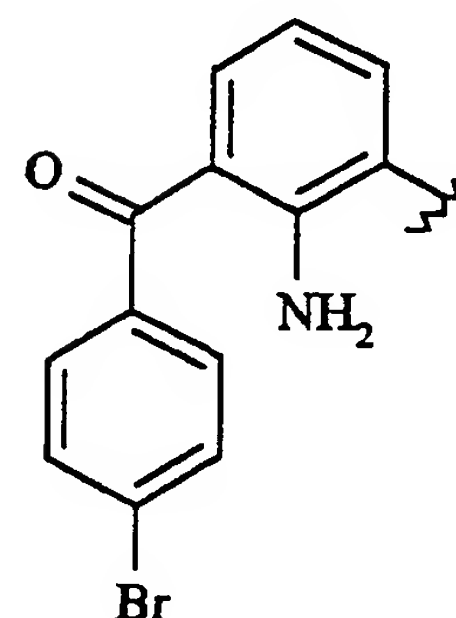
(XXXIII)



(XXXVI)



(XXXVII)



(XII)

wherein the meanings are the following:

- when R_{1a} is as defined in formula (IV), Ketoprofen residue:

R_{III1} is H, SR_{III3} wherein R_{III3} contains from 1 to 4 carbon atoms, linear or branched when possible;

R_{III2} is H, hydroxy;

the compounds wherein R_{III1} and R_{III2} are H, R_{3a} is H, and R_{2a} is methyl, $X = O$, are preferred;

- when R_{1a} is as defined in formula (XXI), carprofen residue:

R_{xx10} is H, linear or branched when possible alkyl from 1 to 6 carbon atoms, C_1-C_6 alkoxy carbonyl linked to a C_1-C_6 alkyl, C_1-C_6 carboxyalkyl, C_1-C_6 alkanoyl, optionally substituted with halogens, benzyl or halobenzyl, benzoyl or halobenzoyl;

R_{xx1} is H, halogen, hydroxy, CN, C_1-C_6 alkyl optionally containing OH groups, C_1-C_6 alkoxy, acetyl, benzyloxy,

SR_{xx12} wherein R_{xx12} is C_1-C_6 alkyl; C_1-C_3 perfluoroalkyl; C_1-C_6 carboxyalkyl optionally containing OH groups, NO_2 ,

amino; sulphamoyl, di-alkyl sulphamoyl with C₁-C₆ alkyl, or difluoroalkylsulphonyl with C₁-C₃ alkyl;

R_{xx1} is halogen, CN, C₁-C₆ alkyl containing one or more OH groups, C₁-C₆ alkoxy, acetyl, acetamido, benzyloxy, SR_{III3} being R_{III3} as above defined, C₁-C₃ perfluoroalkyl, hydroxy, C₁-C₆ carboxyalkyl, NO₂, amino, mono- or di-alkyl-amino C₁-C₆; sulphamoyl, di-alkyl sulphamoyl C₁-C₆, or di-fluoroalkylsulphamoyl as above defined; or R_{xx1} together with R_{xx1} is a C₁-C₆ alkylen dioxy;

the compounds are preferred wherein R_{xx10} is H, the linking group is in position 2, R_{xx1} is H, R_{xx11} is chlorine and is in para position with respect to nitrogen;

R_{3a} is H, R_{2a} is methyl and X is O;

- when R_{1a} is as defined in formula (XXXV), tiaprofenic acid residue:

Ar is phenyl, hydroxyphenyl optionally mono- or polysubstituted with halogen, alkanoyl and alkoxy C₁-C₆, C₁-C₆ preferably C₁C₃ . trialkyl, cyclopentyl, cyclohexyl, cycloheptyl, heteroaryl, preferably thienyl, furyl optionally containing OH, pyridyl;

the preferred compounds of (XXXV) are those wherein Ar is phenyl, R_{3a} is H, R_{2a} is methyl and X is O;

- when R_{1a} is as defined in formula (II), suprofen residue, of which the preferred one has been indicated, wherein R_{3a} is H, R_{2a} is methyl and X = O, as described and obtained in USP 4,035,376 herein incorporated by reference;

- when R_{1a} is as defined in formula (VI), R is the residue of indoprofen when R_{2a} = H and R_{3a} = CH₃; of indobufen when R_{2a} is equal to H and R_{3a} = C₂H₅; X = O, as described and obtained according to USP 3,997,669 herein incorporated by reference;

- when R_{1a} is as defined in formula (VIII), R is the etodolac residue when R_{2a} = R_{3a} = H and X = O, as described and obtained according to USP 3,843,681 herein incorporated by reference;

- when R_{1a} is as defined in formula (VII), R is the fenoprofen residue when R_{3a} = H, R_{2a} = CH₃ and X = O, as described and obtained according to USP 3,600,437 herein incorporated by reference;

- when R_{1a} is as defined in formula (III), R is the fenbufen residue when $R_{2a} = R_{3a} = H$ and $X = O$, as described and obtained according to USP 3,784,701 herein incorporated by reference;
- when R_{1a} is as defined in formula (IX), R is the flurbiprofen residue when $R_{3a} = H$, $R_{2a} = CH_3$, $X = O$;
- when R_{1a} is as defined in formula (X) R is the tolmetin residue when $R_{2a} = R_{3a} = H$, $X = O$, as described and obtained according to FR 1,574,570 herein incorporated by reference;

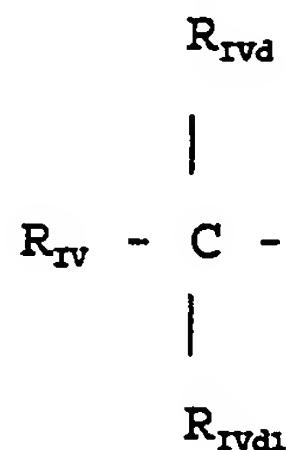
In group IIID) R_{1a} corresponds to the following formulas:

- IIIa), when $R_{2a} = H$ and $R_{3a} = CH_3$, the pranoprofen residue is obtained: α -methyl-5H-[1]benzopyran-[2,3-b]pyridin-7-acetic acid; the preferred compound has $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$;
- (XXX), when $R_{2a} = H$ and $R_{3a} = CH_3$, the bermoprofen residue is obtained: dibenz[b,f]oxepin-2-acetic acid; the preferred compound has $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$.
- (XXXI), when $R_{2a} = H$ and $R_{3a} = CH_3$, R is the radical of the compound CS-670: 2-[4-(2-oxo-1-cyclohexyliden methyl) phenyl]propionic acid; the preferred compound has $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$;
- (XXXII), when $R_{2a} = R_{3a} = H$, the Pemedolac residue is obtained; the preferred compound has $R_{2a} = R_{3a} = H$, $u = 1$ and $X = O$;
- (XXXIII), when $R_{2a} = R_{3a} = H$, the pirazolac residue is obtained: 4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolic acid derivatives;
The preferred compounds have $R_{2a} = R_{3a} = H$, $u = 1$ and $X = O$;
- (XXXVI), when $R_{2a} = H$, $R_{3a} = CH_3$, the zaltoprofen residue is obtained; when the residue is saturated with a hydroxyl or amino group, or with the carboxylic function the compounds are known as dibenzothiepine derivatives; the preferred compounds have $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$;
- (XXXVII), when $R_{2a} = R_{3a} = H$ the mofezolac residue is obtained: 3,4-di(p-methoxyphenyl)isoxazol-5-acetic acid

when the residue is $\text{CH}_2\text{-COOH}$; the preferred compounds have $R_{2a} = R_{3a} = \text{H}$, $t = 1$ and $X = \text{O}$;

- (XII), when $R_{2a} = R_{3a} = \text{H}$ the bromfenac residue is obtained: 2-amino-3-(4-bromobenzoyl)benzeneacetic acid; the preferred compounds have $u = 1$, $t = 1$, $X = \text{O}$, $R_{2a} = R_{3a} = \text{H}$; or $t = 0$;

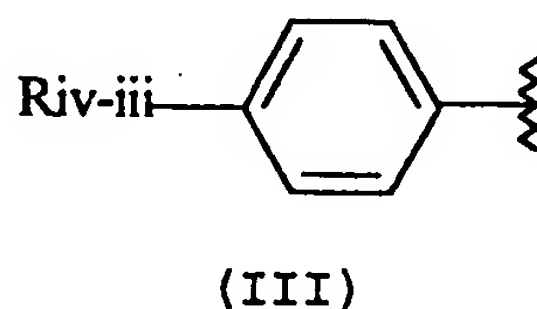
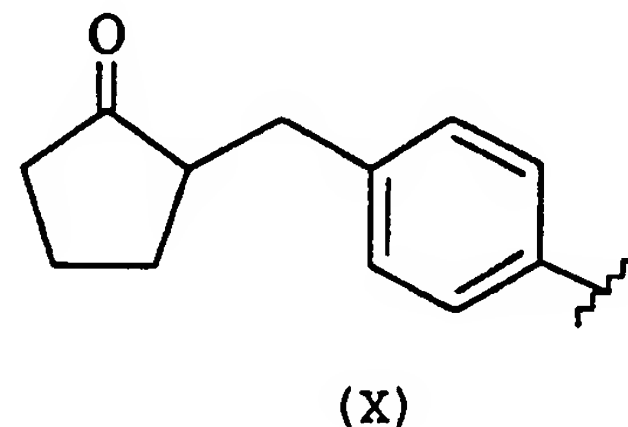
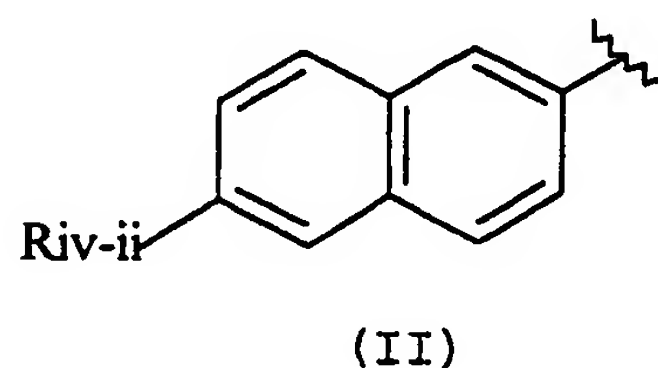
in group IV) wherein $t = 1$, $u = 1$, R is



wherein:

R_{IVd} and R_{IVd1} are at least one H and the other a linear or branched when possible $\text{C}_1 - \text{C}_6$, preferably C_1 and C_2 alkyl, or difluoroalkyl with the alkyl from 1 to 6 carbon atoms, C_1 is preferred, or R_{IVd} and R_{IVd1} form together a methylene group;

R_{IV} has the following meaning:



wherein the compounds of group IV) have the following meanings:

- in formula (II)

$R_{\text{IV-ii}}$ is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_3\text{-C}_7$ cycloalkyl, $\text{C}_1\text{-C}_7$ alkoxyethyl, $\text{C}_1\text{-C}_3$ trifluoroalkyl, vinyl, ethynyl, halogen, $\text{C}_1\text{-C}_6$ alkoxy, difluoroalkoxy, with $\text{C}_1\text{-C}_7$ alkyl, $\text{C}_1\text{-C}_7$ alkoxy-methoxy, alkylthiomethoxy with $\text{C}_1\text{-C}_7$ alkyl, alkyl methylthio with $\text{C}_1\text{-C}_7$ alkyl, cyan, difluoromethylthio,

phenyl- or phenylalkyl substituted with C_1-C_6 alkyl; preferably R_{IV-III} is CH_3O- , R_{IVd} is H and R_{IVd1} is CH_3 , and it is known as naproxen residue;

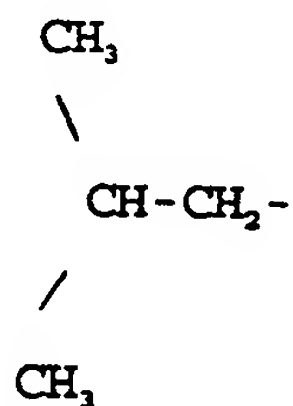
$X = O$ and X_1 is as above defined for Ia);

- in formula (X), of which the loxoprofen residue, described in USP 4,161,538 herein incorporated by reference, has been indicated, the compounds wherein R_{IVd} is H and R_{IVd1} is CH_3 , $X = O$ and X_1 is as above defined for Ia) are preferred;

- in formula (III):

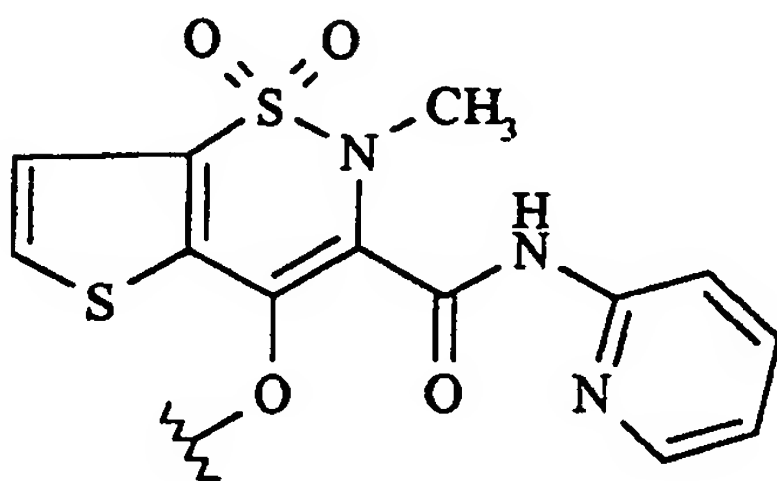
R_{IV-III} is a C_2-C_5 alkyl, optionally branched when possible, C_2 and C_3 alkyloxy, allyloxy, phenoxy, phenylthio, cycloalkyl from 5 to 7 carbon atoms, optionally substituted in position 1 by a C_1-C_2 alkyl;

it is preferred the compound wherein R_{IV-III} is

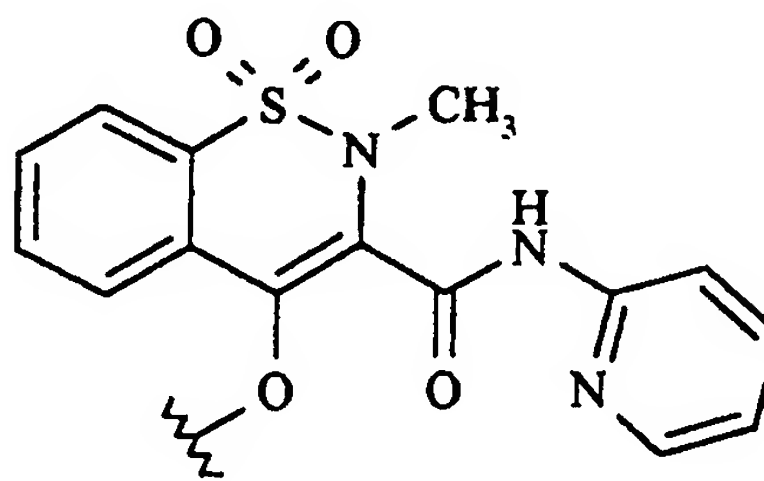


and $R_{IVd} = H$, R_{IVd1} is CH_3 , compound known as ibuprofen residue; $X = O$ and X_1 is as above defined for Ia);

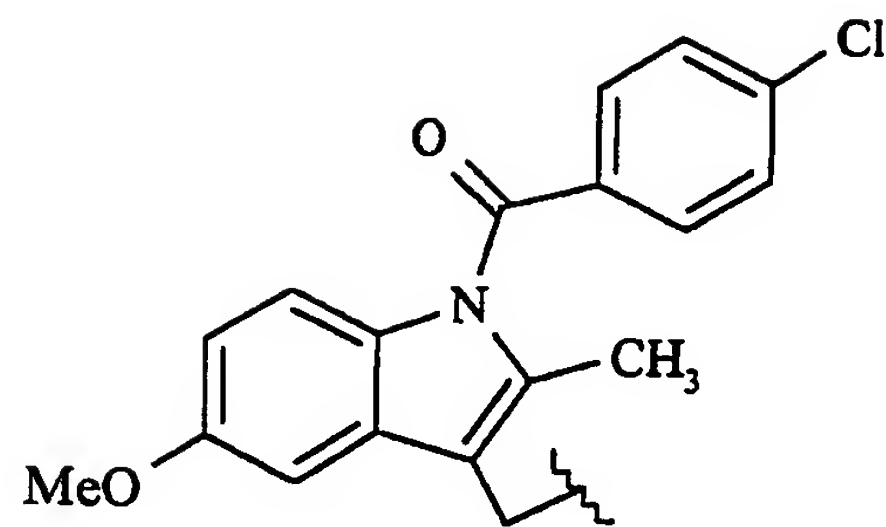
Group V)



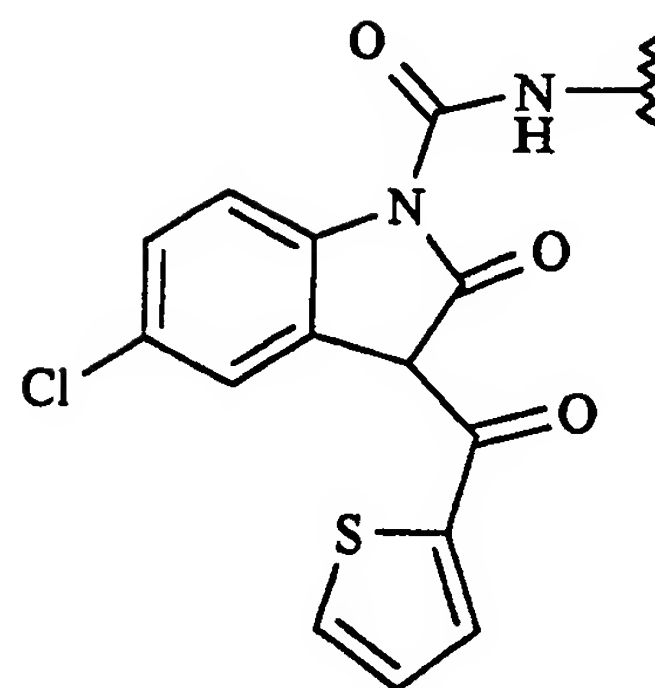
(VII)



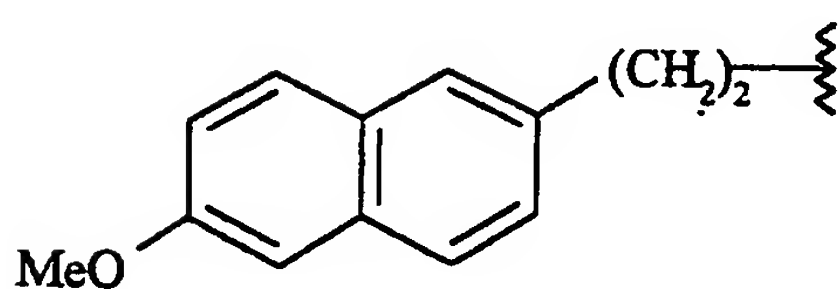
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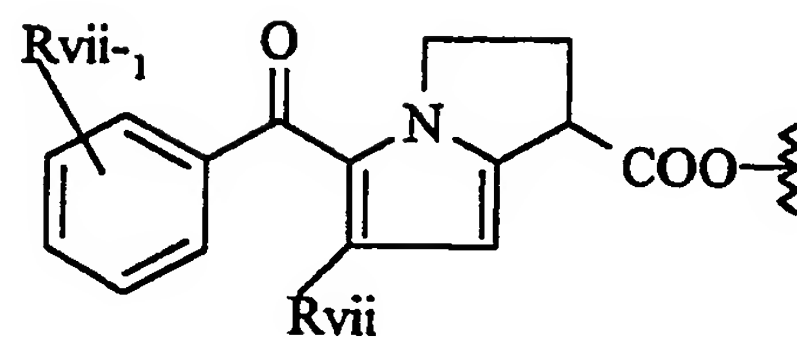
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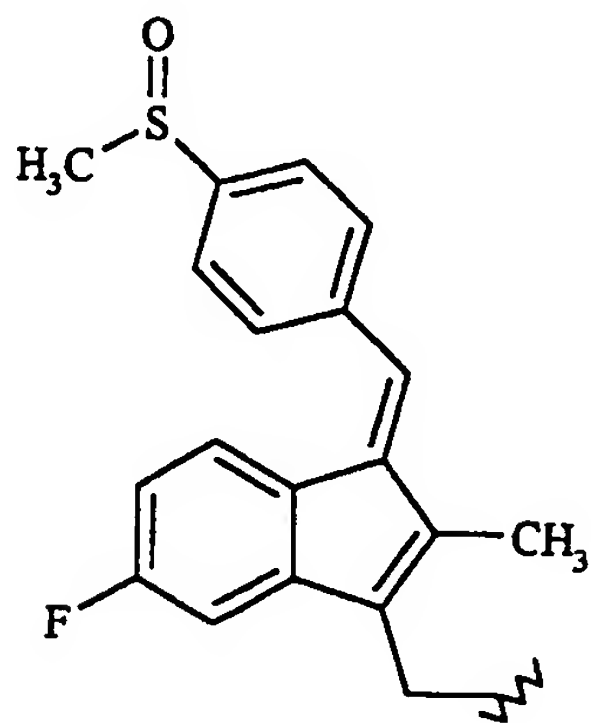
(V)



(III)

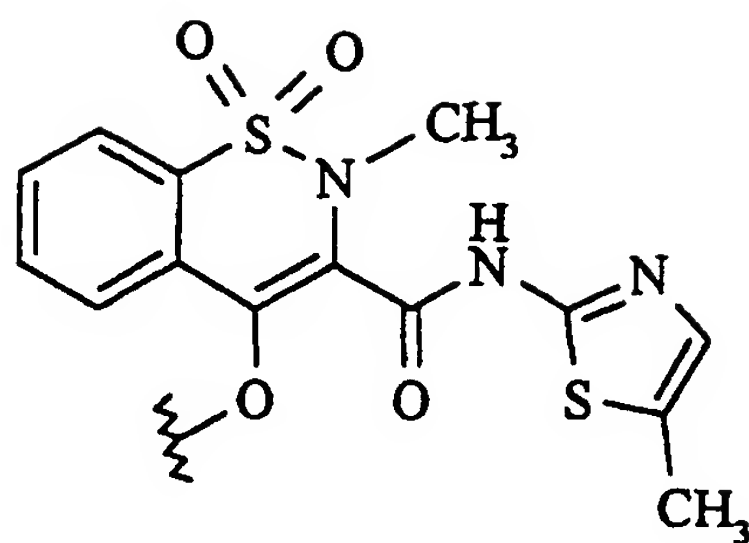


(II)

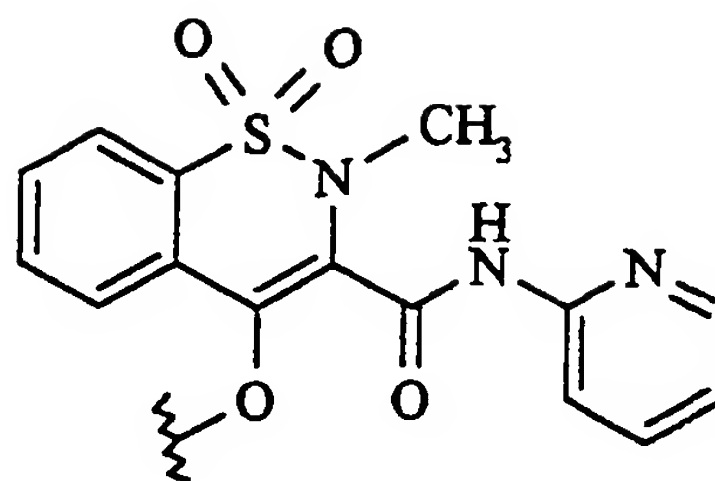


(LX)

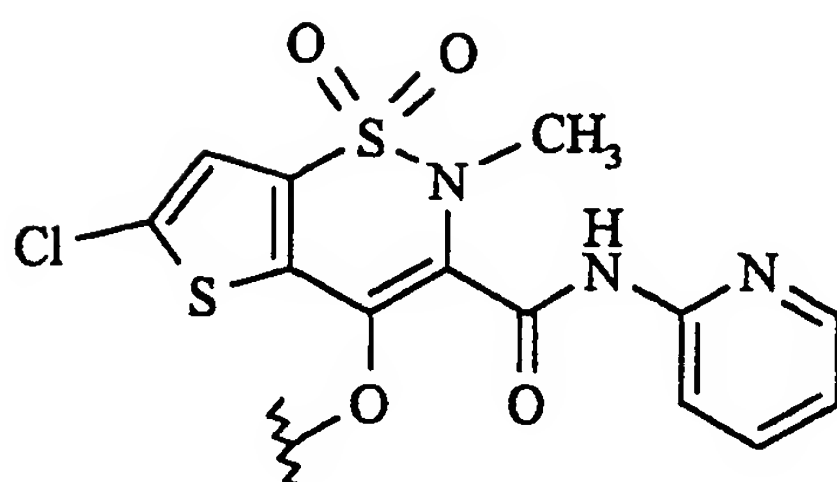
Group VE)



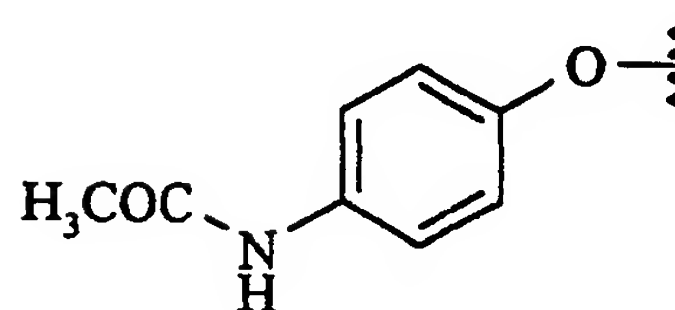
(X)



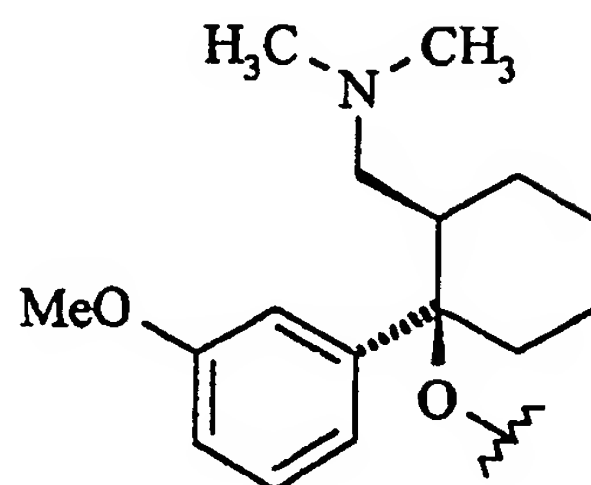
(XI)



(XIII)



(XXXX)



(XXXXI)

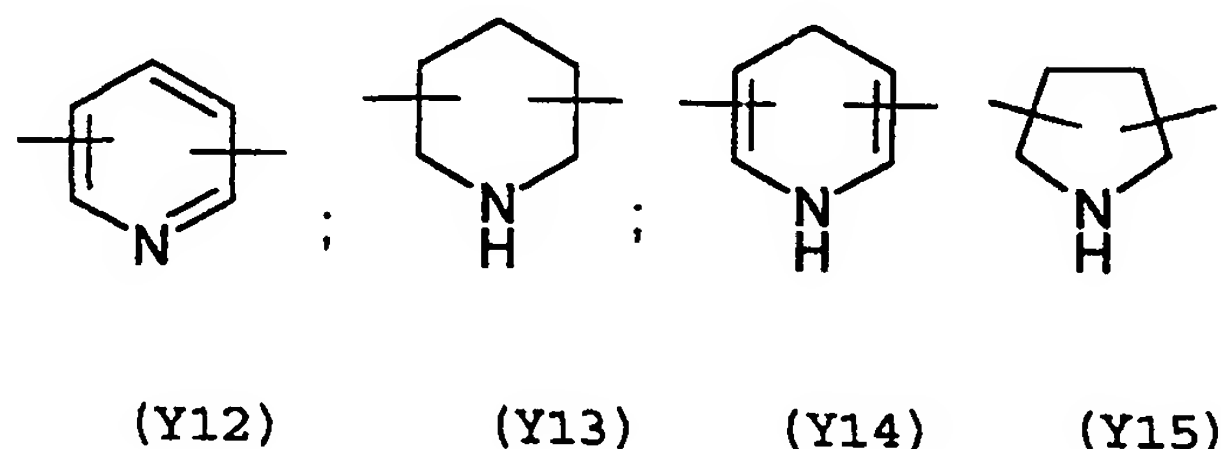
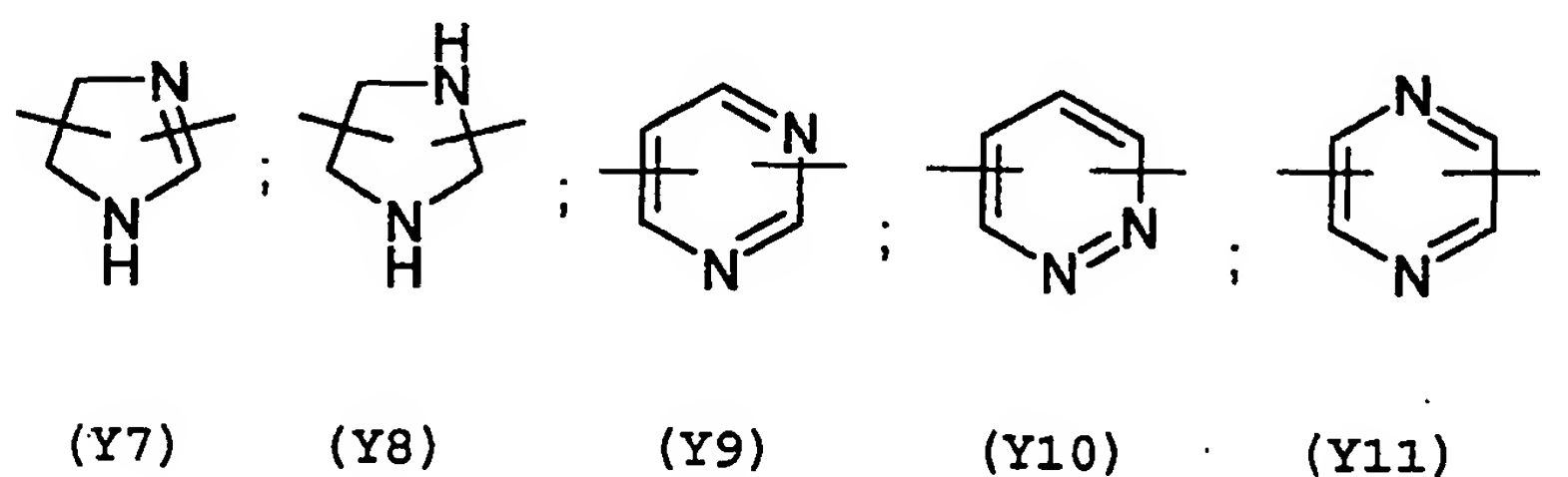
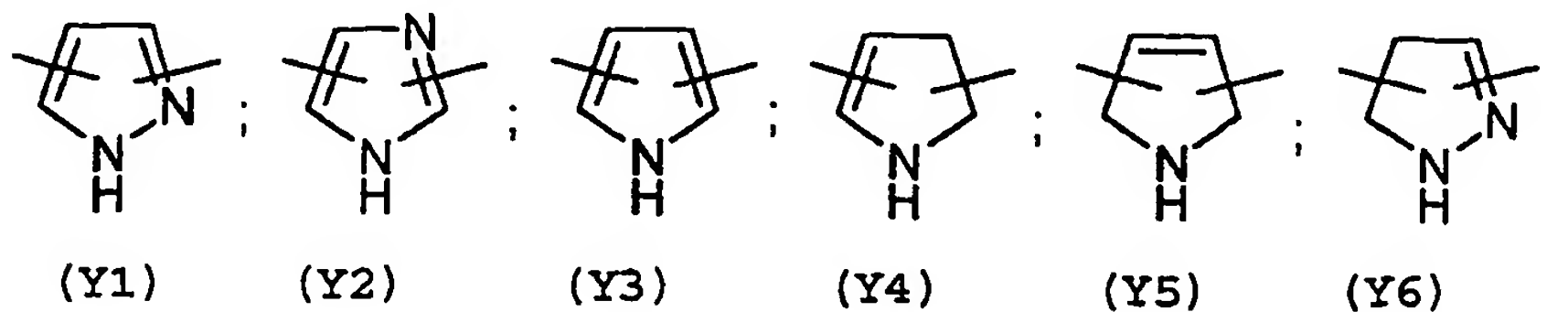
in group V), the compounds have the following meanings:

- when R is formula (II),
 R_{VII} is H or a linear or branched when possible C_1-C_4 alkyl;
 R_{VII-1} is R_{VII} , or a linear or branched when possible C_1-C_4 alkoxy; Cl, F, Br; the position of R_{VII-1} being ortho, or meta, or para;
 the residue of the known Ketorolac is preferred, wherein R_{VII} and R_{VII-1} are H, and $A = R$ (A being the group of the formula $A-X_1-NO_2$) and $t = 0$;
- when R is formula (V),
 of which the residue of the known tenidap has been indicated, as described and obtained in USP 4,556,672

- herein incorporated by reference;
in these compounds of formula (V) $A = R$ and $t = 0$,
- when R is formula (VII),
of which the residue of the known tenoxicam has been indicated, A is RCO , $t = 1$ $u = 0$ or A is R and $t = 0$, as described and obtained in DE 2,537,070 herein incorporated by reference;
 - when R is formula (IX),
wherein $A = R$ and $t = 0$, or $A = RCO$ with $t = 1$ and $u = 0$, the residue of the known piroxicam has been indicated, as described and obtained in USP 3,591,584 herein incorporated by reference;
 - when R is formula (III)
wherein $A = RCOO$, $t = 1$ and $u = 0$ or 1 ; or $t = 0$ and $A = R$, of which the residue of the known nabumetone has been indicated, as described and obtained in USP 4,061,779 herein incorporated by reference;
 - when R is formula (IV)
wherein $A = RCOO$, $t = 1$ and $u = 1$,
of which the indomethacin residue has been indicated, as described and obtained in USP 3,161,654, herein incorporated by reference;
 - when $R =$ formula (LX) and in $(COX)_t$, $u = t = 1$ and X is oxygen, the precursor compound is known as sulindac;
 - when R is formula (X), the X residue is known as meloxicam; the preferred compounds are those wherein $A = RCO$, $t = 1$ and $u = 0$;
 - when R is formula (XI) the residue is known as ampiroxicam when the termination is $-CH(CH_3)OCOC_2H_5$; the preferred compounds have $A = RCO$, $t = 1$ and $u = 0$;
 - when R is formula (XIII) and the valence is saturated with H , the residue derives from lornoxicam; the preferred compounds have $A = RCO$, $t = 1$ and $u = 0$;
 - when R is formula (XXXX) and the valence is saturated with H the compound known as paracetamol is obtained, as described and obtained in USP 2,998,450 herein incorporated by reference;
 - when R is formula (XXXXI) and the valence is saturated with H , the compound known as Tramadol is obtained, as described and obtained in USP 3,652,589;

the preferred compounds according to the present invention obtainable with the radicals corresponding to the formulas (XXXX) and (XXXXI) have $A = RCO$, $t = 1$ and $u = 0$.

Preferably Y is selected from the following:



Preferably Y is an aromatic ring having 6 atoms, containing one nitrogen atom, said aromatic ring having the two free valences in position 2 and 6.

The preferred of Y is Y12 (pyridyl) substituted in position 2 and 6. The bonds can be also in a non symmetric position, for example Y12 (pyridyl) can be substituted also in position 2 and 3; Y1 (pyrazol) can be 3,5-disubstituted.

The X_1 precursors as defined by formula (B), wherein the free valence of the oxygen is saturated with H and the free valence of the end carbon is saturated either with a carboxylic or hydroxyl group, are commercially available compounds or they can be obtained by known methods of the prior art.

The compounds containing R of group I of the type Ia) are described in patent application WO 92/01668 wherein also

the preparation methods are mentioned. This patent is herein incorporated by reference. The compounds of type Ib) are for example prepared by using the method indicated in The Merck Index, XI ed., 1989, pag. 16, No. 95 for the acetylsalicylsalicylic acid residue. The modifications of the compounds of formula Ib) can be obtained by using the processes mentioned in patent application WO 92/01668.

The compounds wherein R is of group II) are described in patent application WO 94/04484 and USP 3,558,690 wherein also the preparation methods are indicated. These patents are herein incorporated by reference.

The starting compound of IIb), when the valence is saturated with -COOH (flunixin), is obtained according to USP 3,337,570 and USP 3,689,653, both herein incorporated by reference. The compounds containing the substituents mentioned in the previous patents are equivalent to flunixin.

The compounds wherein R is of group III) are described and obtained by the processes mentioned in the following patents:

patent application PCT/EP/93 03193; for the compounds of formula (IV) see also USP 3,641,127; for the compounds of formula (XXI) see also USP 3,896,145; for the compounds of formula (IX) flurbiprofen residue see also USP 3,755,427; for the compounds of formula (II) see also USP 4,035,376; for the compounds of formula (VI) see also USP 3,997,669; for the compounds of formula (VIII) see also USP 3,843,681; for the compound of formula (VII) see also USP 3,600,437; for the compounds of formula (III) see also USP 3,784,701. All these mentioned patents are herein incorporated by reference.

The procedures for the preparation of the compounds of class IIID) are the following:

The residue IIIa) is obtained by preparing the acid compound according to USP 3,931,205, the valence is saturated with -CH(CH₃)-COOH. The compounds containing the substituents mentioned in the previous patent are equivalent to pranoprofen. The residue (XXX) is prepared through the compound with the group -CH(CH₃)-COOH (bermoprofen) according to USP 4,238,620 herein incorporated by reference. Other equivalent products are described in the above mentioned patent.

The residue (XXXI) is prepared by starting from the corresponding acid $-\text{CH}(\text{CH}_3)-\text{COOH}$ according to USP 4,254,274. Equivalent compounds are described in the same patent.

The residue (XXXII) is prepared according to EP 238,226 herein incorporated by reference, when the valence is saturated with $-\text{CH}_2-\text{COOH}$. Equivalent products are reported in said patents as 1,3,4,9 tetrahydropyran [3,4-b] indol-1-acetic substituted acids.

The residue (XXXIII) is prepared from pirazolac and the valence is saturated with $-\text{CH}_2-\text{COOH}$, as indicated in EP 54,812 herein incorporated by reference. Equivalent products are described in said patent.

The residue (XXXVI) is prepared according to UK 2,035,311 herein incorporated by reference, by starting from zaltoprofen and having the $-\text{CH}(\text{CH}_3)-\text{COOH}$ termination. Equivalent products are described in said patent.

The process for preparing the residue (XXXVII) is obtained by starting from mofezolac and it is prepared according to EP 26,928. Equivalent products are reported in the same patent.

The compounds wherein R is of group IV) are described in GB patent application 2,283,238, wherein also the preparation methods are indicated; this patent is herein incorporated by reference.

In group IV) the compounds can also be obtained: for the compounds of formula (II) using USP 3,904,682; the compounds of formula (X) according to USP 4,161,538; the compounds of formula (III) according to USP 3,228,831. The herein mentioned patents are incorporated in the present application by reference.

In group V) the compounds can also be obtained: for the compounds of formula (II) using USP 4,089,969 herein incorporated by reference; the compounds of formula (V) can be obtained according to USP 4,556,672 herein incorporated by reference.

The residue (X) is prepared according to the German patent 2,756,113. Equivalent products are described in said patent.

The residue (XI) is prepared according to EP 147,177, herein incorporated by reference, starting from ampiroxicam

having the termination $-\text{CH}(\text{CH}_3)\text{OCOOC}_2\text{H}_5$. Equivalent products are described in said patent.

The residue (XII) is prepared according to J. Med. Chem., vol. 27 No. 11, Nov. 1984, Walsh et Al. "Antiinflammatory Agents. 3. Synthesis and Pharmacological Evaluation of 2-amino-3-benzoylphenylacetic Acid and Analogues", herein incorporated by reference. Equivalent products are described in said publication.

The residue (XIII) is prepared starting from lornoxicam, wherein the valence is saturated with H. It is prepared according to GB 2,003,877. Equivalent products are described in said patent.

The residue (LX) in group V is prepared from Sulindac, obtained according to US 3,654,349.

In general the connection between A and X_1 is, as seen, of ester or amidic type (NH or NR_{1c} , as defined in X) when R is of groups I, II, III, IV and V. For the formation of such connection all the synthesis routes well known for the formation of such bonds are usable.

The preparation of the compounds of formula $\text{A-X}_1\text{-N(O)}$, with the linking group X_1 of formula (B) is described in published PCT application WO 00/51988 in the name of the Applicant, herein incorporated by reference.

The compounds inhibiting the phosphodiesterase C) salified with nitric acid are selected from the following:

(C1) 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazol[4,3-d]-pyrimidin-5-yl)-phenyl]sulphoyl]-4-methyl-piperazine (Sildenafil), (C2) 2-(2-propyloxyphenyl)-8-azapurin-6-one (Zaprinast), (C3) 2,6-bis-(diethanolamino)-4,8-dipiperidine pyrimido [5,4-d]-pyrimidine (dipyridamol), (C4) 6-chloro-4-(1,3-dioxaindan-5-yl)methylamino-2(4-carboxy-1-piperidinyl)-quinazoline, (C5) N-(phenylmethyl)-1-ethyl-1H-pyrazol-[3,4-b]-quinolin-4-amine, (C6) 1-(2-chlorobenzyl)-3-isobutyryl-2-propyl-6-aminocarbonyl-indol, (C7) 1-benzyl-6-chloro-2-[1-[3-(imidazol-1-yl)propyl]indol-5-yl-amino carbonyl]benzimidazol, (C8) 2-(1-imidazolyl)-5-(phenyl)-4-(1,3-dioxaindan-5-yl)methyl aminopyrimidine, (C9) 6-ethynyl-4-(2-methoxyethyl)amino-2-(1-imidazolyl)quinazoline, (C10) 1-cyclopentyl-3-ethyl-6-(2-propoxyphenyl)pyrazol[3,4-d]pyrimidin-4-one, (C11) 1-cyclopentyl-3-ethyl-6-(4-methoxybenzyl)-pyrazol-

[3,4-d]-pyrimidin-4-one, (C12) 1,3-dimethyl-6-(2-propoxy-5-methansulphonamidophenyl)-1,5-dihydro pyrazol[3,4-d]-pyrimidin-4-one, (C13) (6R, 12aR)-2,3, 6,7,12, 12a-hexahydro-2-methyl-6-(1,3-dioxan-5-yl)pyrazin [2',1':6,1] pyrido[3,4-b]indol-1,4-dione, (C14) 1-propyl-3-methyl-6-[2-propoxy-5-[(4'-methyl-1-pyrazinyl)sulphonamido] phenyl]-1,5-dihdropyrazol[3,4-d]pyrimidin-4-one, (C15) 3-(4-amino carbonyl-1-piperidinyl)-6-cyan-8-(3-chloro-4-methoxy-phthalazine, (C16) 2-(1-imidazolyl)-4-(1,3-dioxaindan-5-yl) methylamino-7,8-dihydro-5H-thiopyran[3,2-d]pyrimidine, (C17) 1-Cyclopentyl-3-ethyl-6-(3-ethoxypyrid-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-one, (C18) 1-[3-[1-[(4-Fluorophenyl)methyl]-7,8-dihydro-8-oxo-1H-imidazo[4,5-g]quinazolin-6-yl]-4-propoxyphenyl] carboxamide.

The pharmaceutical formulations usable for the specific use according to the present invention are those well known to the skilled in the art and which can be prepared according to the texts widely known in the prior art. See for example the volume "Remington's Pharmaceutical Sciences 15a Ed."

The dosages of the salts of the invention in their pharmaceutical compositions are equal, and generally lower than those of their precursors of the above mentioned classes, said salts generally being more effective and better tolerated.

The salts of the compounds A) and C) can be used as such, preferably in formulations administrable according to conventional administration routes of drugs. For example they can be administered by systemic route, for example by oral, sublingual route.

Surprisingly it has been found by the Applicant that the sildenafil nitrate has a power ratio, calculated as ratio between the myorelaxing effect on the cavernous body and the systemic pressure effect (see the data on the aorta reported in Table 1), clearly in favour of the myorelaxing effect. This shows that the sildenafil nitrate can be used for the impotence treatment also by cardiopathic people since the pressure effect (aorta) is very reduced.

For patients suffering from sex dysfunctions (male and female) it has been found that the salts of compounds A) and the nitrate salts of compounds C) for systemic use have a low

pressure effect wherefore the power ratio, calculated as above, is improved with respect to the commercial sildenafil (citrate salt).

It has been unexpectedly found that the salts of the compounds of the invention can also be topically administered as such, preferably using the corresponding formulations containing them as active principles. This is a surprising fact since it is not said that a compound active by systemic route is active also by topical route. It has been unexpectedly found that also the salts of compounds C), different from nitrates, are active by topical route, as such or when administered carried in the above formulations.

Examples of organic salts of C) are oxalate, tartrate, maleate, succinate, citrate, glycinate, lysinate; examples of inorganic anions are nitrate, chloride, sulphate, phosphate.

The administration by topical route of compounds A) and of the salts of C), in particular of the phosphodiesterase inhibitors, was not predictable for the use according to the present invention, in particular for the treatment of the male impotence and of the female sex dysfunctions, since the myorelaxing action of said products is not direct but it takes place through the strengthening of the endogen mediator cGMP which is formed through the nitric oxide.

In particular, as regards the compositions for topical use, the salt amount of the compounds of classes A) and C) in the pharmaceutical form, for the predicted use according to the present invention, is in the range 0.5-10%, preferably 2-6%, as percentage by weight on the total weight of the composition. Said formulations for topical use can be in the form of salves, creams and gels and are prepared according to the techniques known to the skilled of the art, as described for example in the above mentioned volume.

The above compounds inhibiting the phosphodiesterases are synthesized as described in the following references (C1): G.B. 92480; (C2): DE 2162096; (C3): The Merck Index 12th Ed.; (C4): WO 9422855; (C5): WO 9628159; (C6): WO 9632379; (C7): WO 9703070; (C8): USP 5,525,604; (C9): USP 5,436,233; (C10): WO 9628448; (C11): WO 9628429; (C12): EP 636626; (C13): WO 9519978; (C14): EP 636626; (C15): WO 9605176; (C16): EP

728759; (C17): US 5,294,612; (C18): J. Med. Chem. 2000, 43, 1257-1263.

Constitutes a further object of the present invention nitrooxy derivatives of the following phosphodiesterase inhibitors:

- (C2) 2-(2-propyloxyphenyl)-8-azapurin-6-one (zaprinast),
- (C3) 2,6-bis-(diethanolamino)-4,8-dipiperidine pyrimido [5,4-d]-pyrimidine (dipyridamol),
- (C4) 6-chloro-4-(1,3-dioxaindan-5-yl)methylamino-2(4-carboxy-1-piperidinyl)-quinazoline,

of formula:

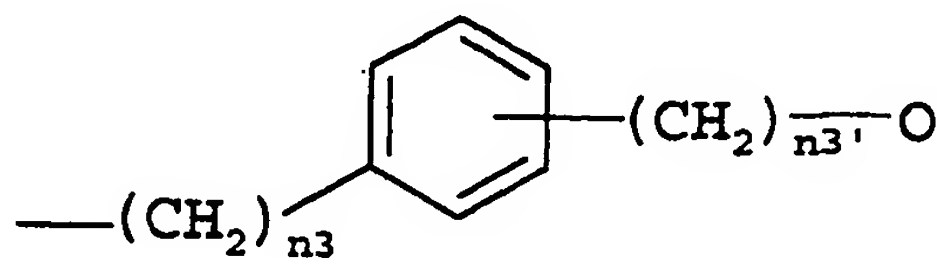


Wherein A is as above defined, and

- in the case of (C2) $t = 0$ and R is the phenyloxy radical derived by substituting the ether group on the phenyl ring of Zaprinast with an hydroxy function (see Tetrahedron letters 1967 pages 4131 and following ones, Tetrahedron letters 1968 24 pages 2289 and following ones);
- in the case of (C3) $t = 0$ and R is the alcoxy radical derived from the precursor;
- in the case of (C4) $t = u = 1$ and X is oxygen;

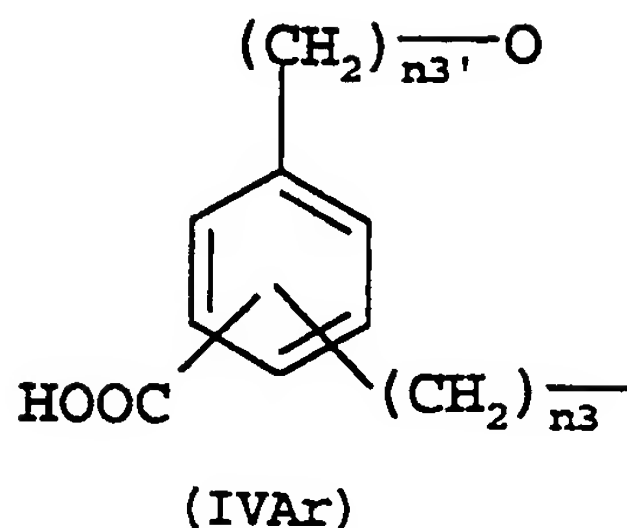
X_{1A} can have the meaning of X_1 above and also the following ones:

- an alkylene group R' wherein R' is a C_1-C_{20} linear or branched when possible, preferably having from 2 to 6 carbon atoms, optionally substituted with one or more of the following groups: $-NHCOR_3$, wherein R_3 is C_1-C_4 linear or branched alkyl, $-NH_2$, or OH
- a cycloalkylene having from 5 to 7 carbon atoms, optionally substituted with side chain R' , R' being as above, one or more carbon atoms of the cycloalkylene ring can optionally be substituted by heteroatoms;

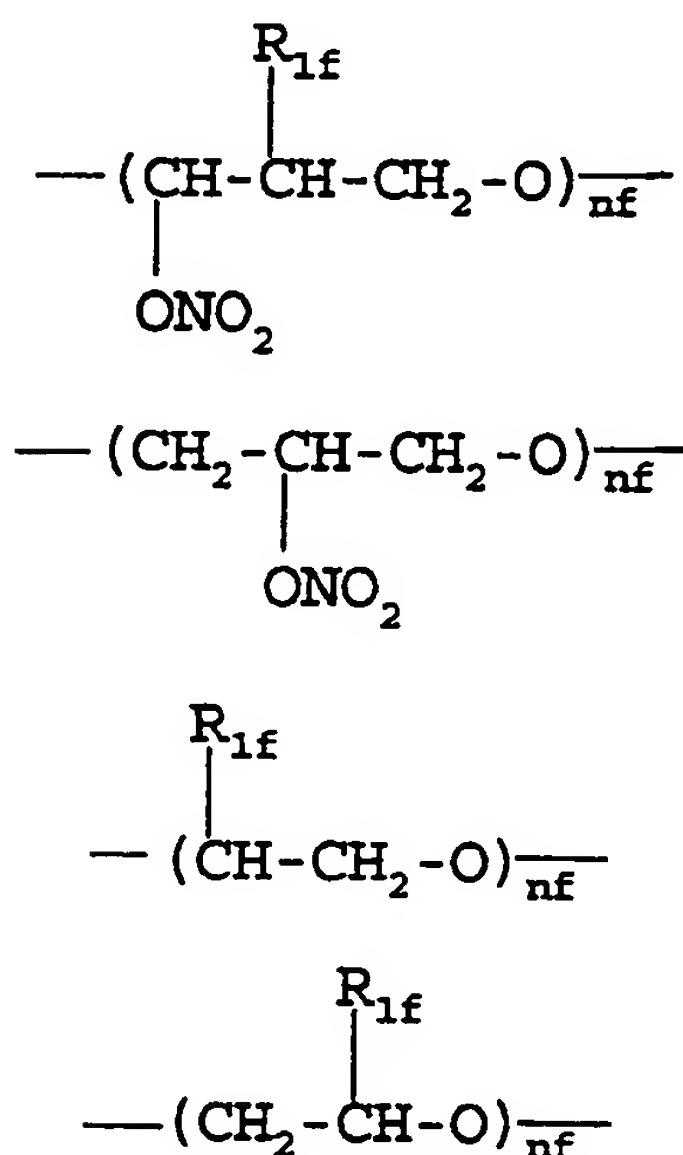


(IIIa)

wherein n_3 is an integer from 0 to 3 and n_3' is an integer from 1 to 3;



wherein n_3 and n_3' have the above meaning;



wherein $\text{R}_{1f} = \text{H}, \text{CH}_3$ and nf is an integer from 1 to 6, preferably from 1 to 4.

The compounds of formula (IC) as above defined can be prepared with known methods; when the bivalent linking bridge is of formula (B), the same methods above described apply. When the linking bridge have the other meanings the methods described in WO 95/30641.

The nitrate salts of the phosphodiesterase inhibitors can be prepared by known methods, for example as described in the patent application WO 99/67231; the other salts of compounds C) with anions different from nitrate are prepared by known methods of the prior art, such as for example described in patent application WO 96/28448.

The following Examples illustrate the invention but they do not limit the scope thereof.

EXAMPLE 1

Preparation of a formulation for topical use containing as active principle the 2(acetyloxy)benzoic acid 6-(nitroxymethyl)-2-methylpyridyl ester hydrochloride (NCX 4050).

The compound is prepared according to Example 1 of patent application PCT/EP 00/01454.

Components of the formulation for topical use:

NCX 4050	4.2 g
white vaseline	24 g
cetostearyl alcohol	9.5 g
polyoxyethylene (60 OE) sorbitan monostearate (Polysorbate® 60)	4.8 g
glycerine	9.5 g
purified water	48 g
total	100 g

Preparation of the formulation

In a weighed vessel the white vaseline (24 g) and the cetostearyl alcohol (9.5 g) are melted. To the melted mass (70°C) a solution previously obtained by dissolving NCX 4050 (4.2 g), polysorbate® 60 (4.8 g) and glycerine (9.5 g) in fresh-boiled purified water is added under stirring. At the end of the addition one continues to stir until complete cooling of the mass and at last it is determined by weighing the evaporated water amount, which is added to the formulation until obtaining the required total weight (100 g).

PHARMACOLOGICAL EXAMPLES

EXAMPLE F1

The relaxing effect of the tested drugs on cavernous body tissues has been evaluated with experiments in vitro as a measure of the inhibiting action on the impotence, and on aorta tissues as expression of the undesired hypotensive effect.

Preparation of tissues

White New Zealand rabbits were sacrificed, cavernous body and aorta specimens were taken and suitably prepared for the determination of the myorelaxing activity in vitro, according to the procedure described by J. Jeremy (Br. J. Urology 79, 958-63, 1997).

The tissues were precontracted with phenylephrine (10 μ M) and the relaxation was determined in the presence of the compounds object of the invention.

The compounds examined in this test are reported in Table 1. The 2-(acetyloxy)benzoic acid 6-(nitroxy methyl)-2-methylpyridyl ester hydrochloride (NCX 4050) is prepared as described in patent application PCT/EP 00/01454 (Ex. 1), the sildenafil nitrate has been prepared as described in patent application WO 99/67231 (Ex. 3). The products used in the experiment were dissolved in dimethylsulphoxide, except sodium nitroprussiate which was dissolved in distilled water.

The data of the Table show that the products of the invention are more effective than the reference substances in relaxing the cavernous body, and induce a lower vasorelaxing effect on the aorta.

EXAMPLE F2

The effect of the sildenafil citrate and sildenafil nitrate on the aorta relaxation was evaluated with an experiment in vitro in the presence of a conventional NO-donor (sodium nitroprussiate). Under these conditions it is known that the sildenafil citrate causes hypotension.

The experiment was carried out as described in the previous Example, by using aorta tissues taken from white New Zealand rabbits. The tissue strips are treated first with sodium nitroprussiate 10^{-7} M, then a part of the strips was treated with sildenafil citrate 10^{-7} M and another part with sildenafil nitrate 10^{-7} M.

The results of the experiment are reported in Table 2 and are expressed as percentage of the aorta relaxation with respect to the initial treatment with sodium nitroprussiate and they show that the sildenafil nitrate causes a lower strengthening of the relaxing effect induced by sodium nitroprussiate compared with the sildenafil citrate. Therefore the sildenafil nitrate is less hypotensive than the sildenafil citrate.

Table 1

Experiment in vitro on the myorelaxing effect of the cavernous body and of aorta of the following compounds NCX 4050, sildenafil nitrate, sildenafil citrate and sodium nitroprussiate as a comparison.

Treatment	Concentration (M)	Cavernous body % relaxation	Aorta %	Power ratio
NCX 4050	10 ⁻⁶	80	80	1
Sodium Nitroprussiate	10 ⁻⁶	50	100	0.5
Sildenafil Nitrate	10 ⁻⁶	100	20	5
Sildenafil Citrate	3x 10 ⁻⁵	50	75	0.66

Table 2

Experiment in vitro on the myorelaxing effect on aorta tissues pretreated with sodium nitroprussiate and then treated, respectively, with sildenafil nitrate and sildenafil citrate		
Treatment	Concentration (M)	Aorta relaxation %
Sodium Nitroprussiate	10 ⁻⁷	100
Sildenafil Nitrate	10 ⁻⁷	120
Sildenafil Citrate	10 ⁻⁷	170

CLAIMS

1. Use for the treatment of sex dysfunctions of one or more of the following classes of drugs:

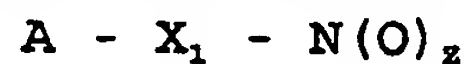
A) salified and non salified nitric oxide donor drugs, of formula



wherein the meaning of the terms appearing in the formula is as defined hereunder;

C) nitrate salts of compounds inhibiting phosphodiesterases;

in the compounds of general formula:

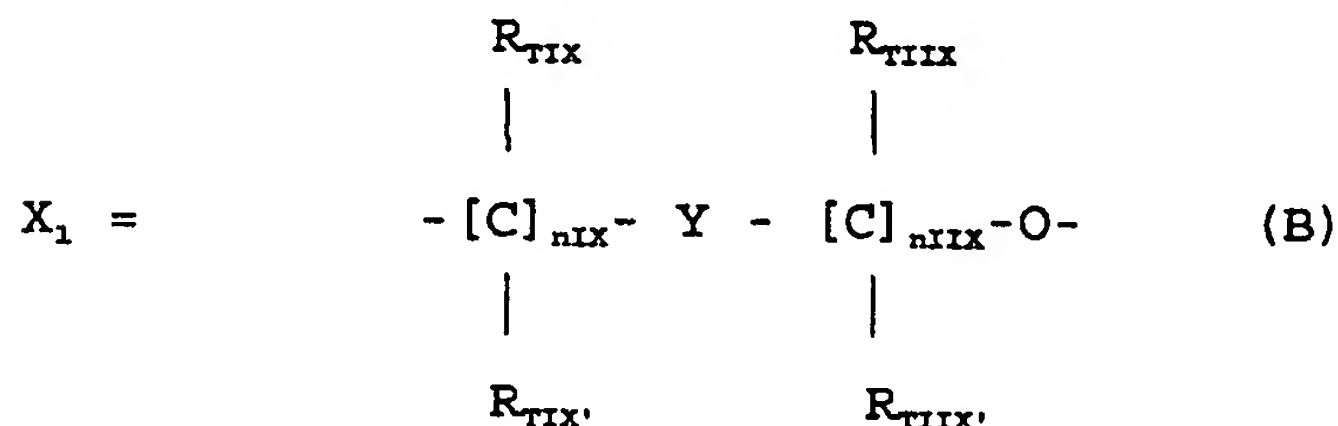


z is an integer and is 1 or 2, preferably 2;

A = $R(COX_u)_t$ and wherein t is an integer 0 or 1; u is 0 or 1;

X = O, NH, NR_{1c} wherein R_{1c} is a linear or branched C_1 - C_{10} alkyl;

X_1 is the following bivalent linking group:



wherein:

nIX is an integer in the range 0-3;

nIIX is an integer in the range 1-3;

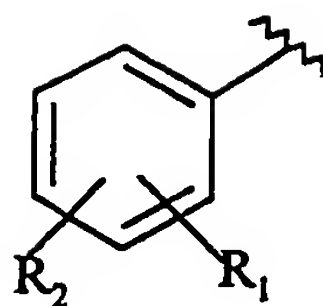
R_{TIX} , $R_{TIX'}$, R_{TIIIX} , $R_{TIIIX'}$, equal to or different from each other are H or a linear or branched C_1 - C_4 alkyl;

Y is an heterocyclic ring containing one or two nitrogen atoms, optionally one oxygen or sulphur atom, said saturated, unsaturated or aromatic ring having 5 or 6 atoms;

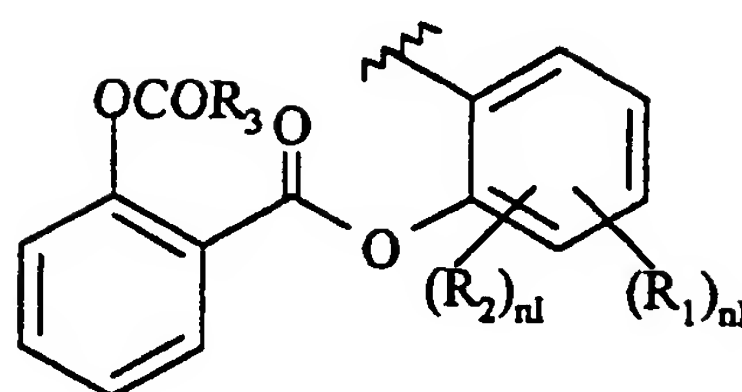
R of the radical A of formula $A - X_1 - N(O)_z$ is selected from the following groups:

Group I) wherein t = 1 and u = 1

Ia)



Ib)



wherein:

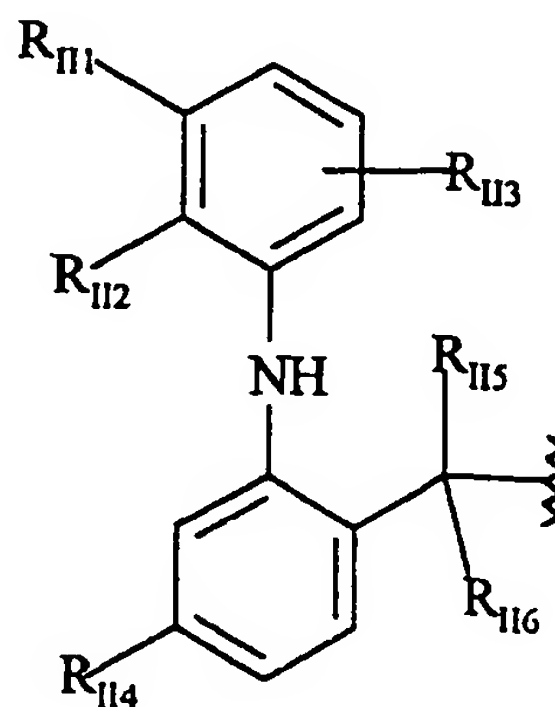
R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or a linear or branched C_3 - C_5 alkyl, or the residue of an heterocycle having only one ring having 5 or 6 atoms which can be aromatic, partially or totally hydrogenated, containing one or more hetero-atoms independently selected from O, N and S;

R_2 is hydrogen, hydroxy, halogen, linear or branched C_1 - C_4 alkyl, linear or branched C_1 - C_4 alkoxy; a linear or branched C_1 - C_4 perfluoroalkyl, for example trifluoromethyl; nitro, amino, mono- or di- (C_{1-4}) alkylamino;

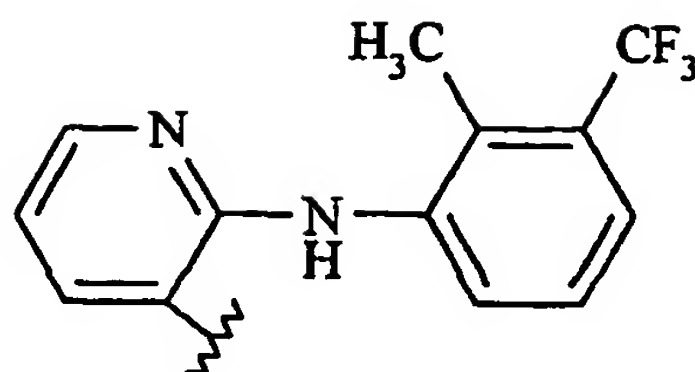
nI is an integer 0 or 1;

group II) wherein $t = 1$, $u = 1$

IIa)



IIb)



wherein:

R_{II5} is H, linear or branched when possible C_1 - C_3 alkyl;

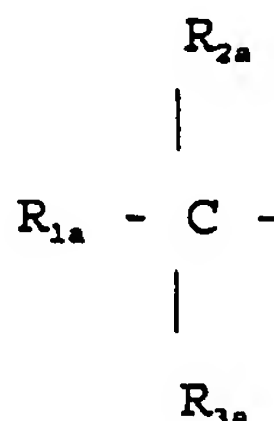
R_{II6} has the same meaning as R_{II5} , or when R_{II5} is H it can be benzyl;

R_{II1} , R_{II2} and R_{II3} can independently be hydrogen, linear or branched when possible C_1 - C_6 alkyl, or linear or branched when possible C_1 - C_6 alkoxy, or Cl, F, Br;

R_{II4} is R_{II1} or bromine;

IIb) is the residue of the 2-[(2-methyl-3-(trifluoromethyl)phenyl)amino]-3-pyridinecarboxylic acid and when the -COOH group is present it is known as flunixin;

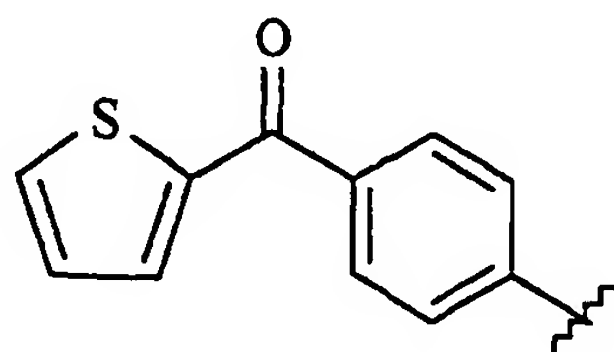
group III) wherein $t = 1$, $u = 1$ and R is



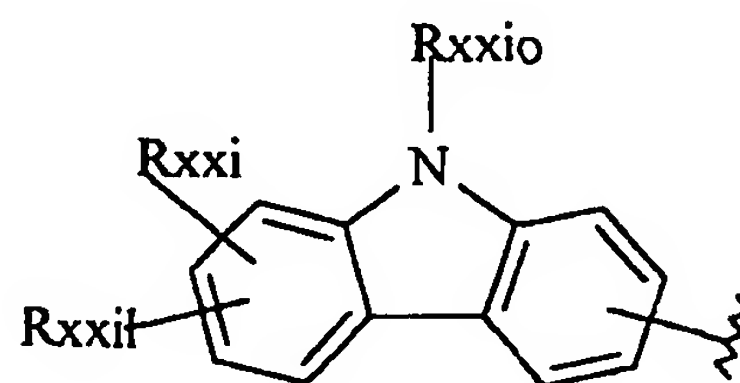
wherein:

R_{2a} and R_{3a} are H, linear or branched when possible, substituted or not, C_1 - C_{12} alkyl or allyl, with the proviso that if one of the two is allyl the other is H; preferably R_{2a} is H, C_1 - C_4 alkyl, R_{3a} is H;

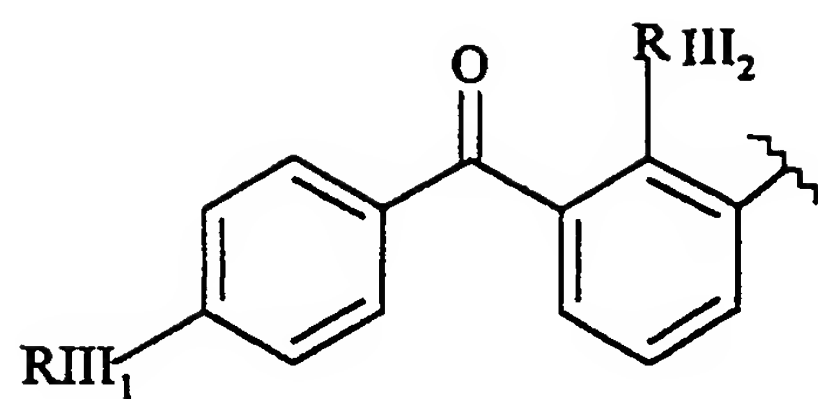
R_{1a} is selected from



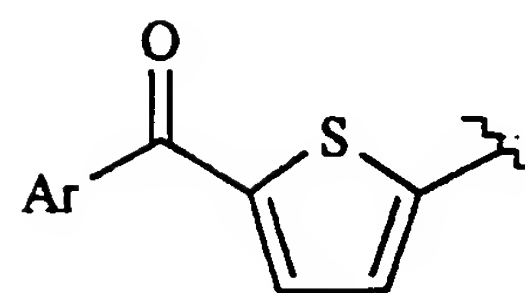
(II)



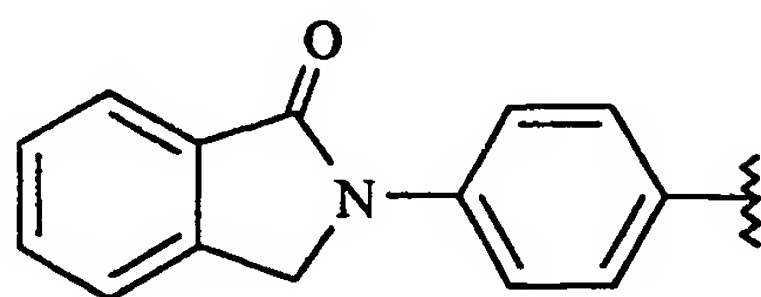
(XXI)



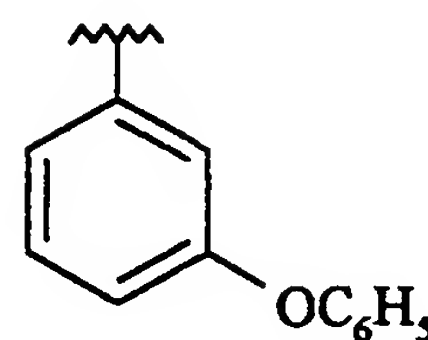
(IV)



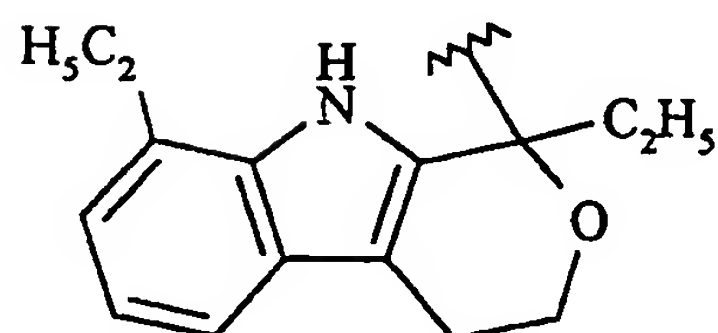
(XXXV)



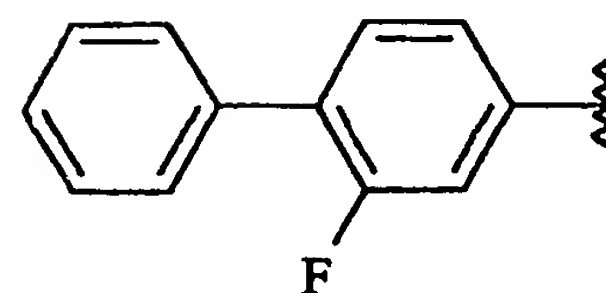
(VI)



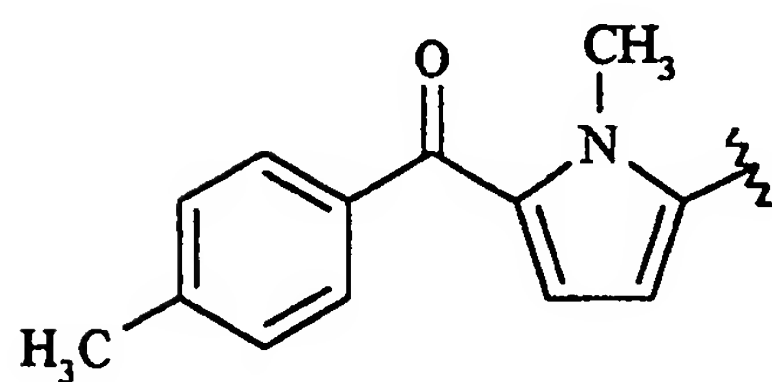
(VII)



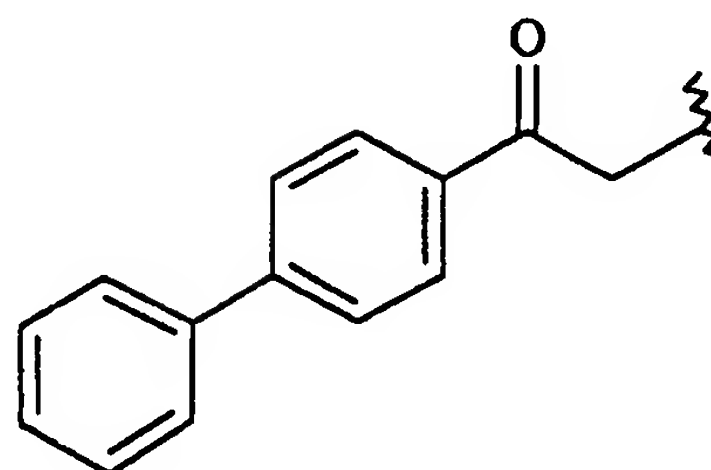
(VIII)



(IX)

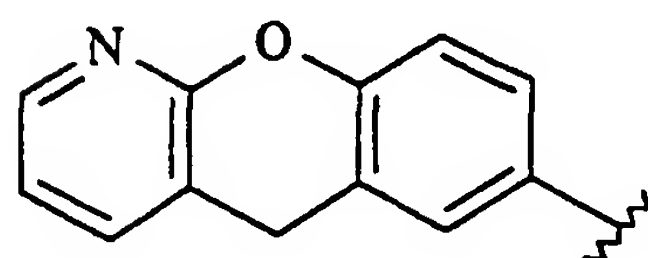


(X)

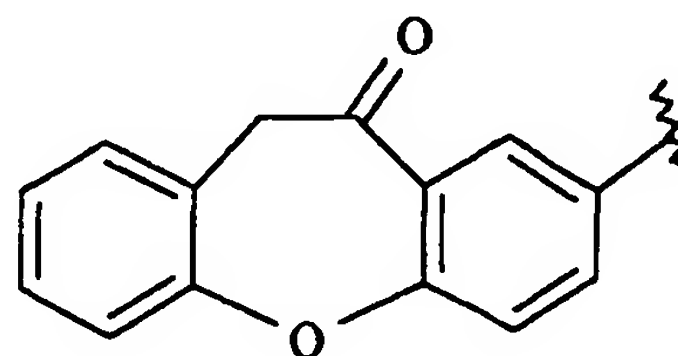


(III)

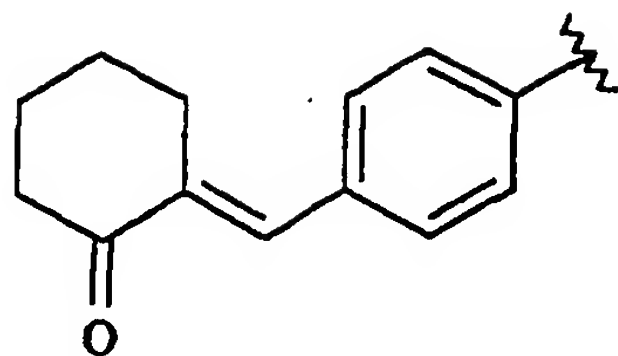
IIID) R_{1a} corresponds to the following formulas:



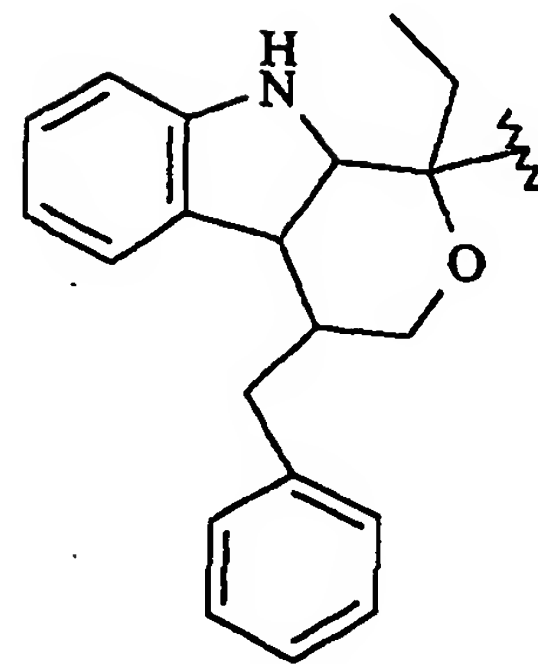
(IIIa)



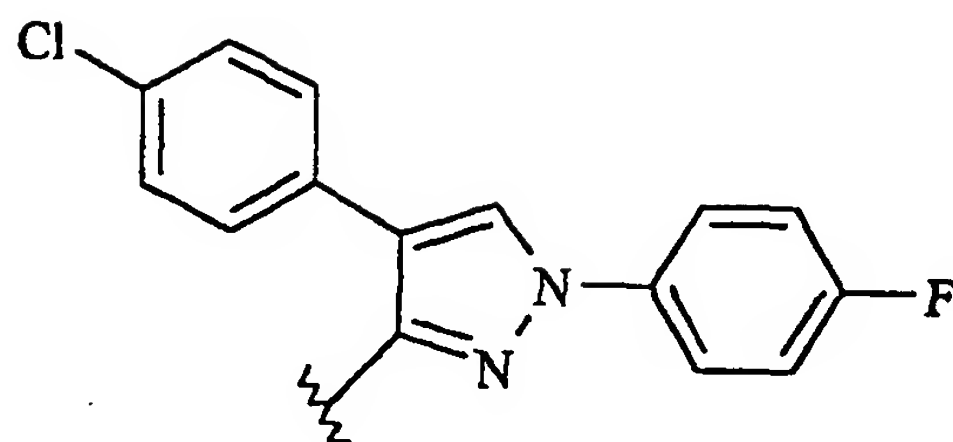
(XXX)



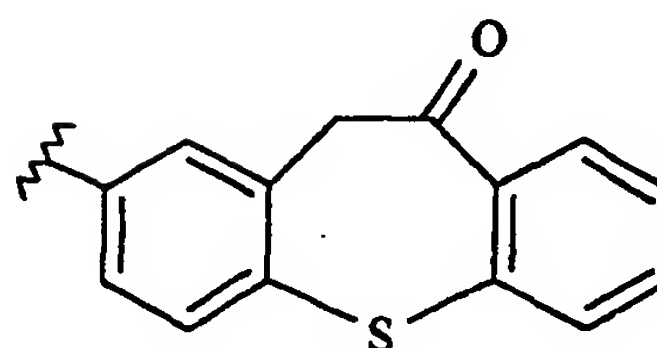
(XXXI)



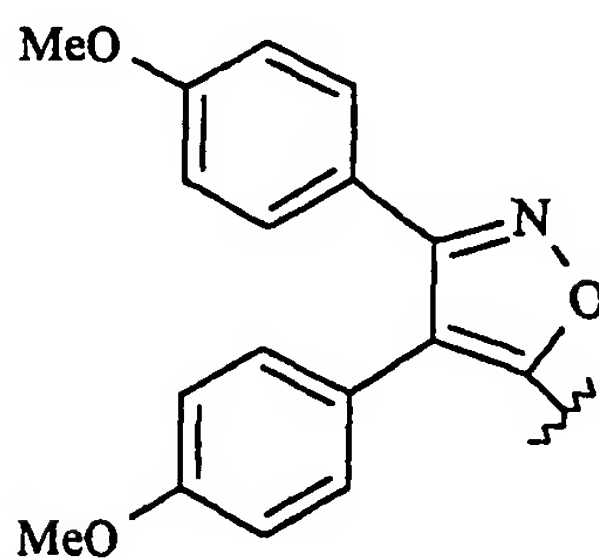
(XXXII)



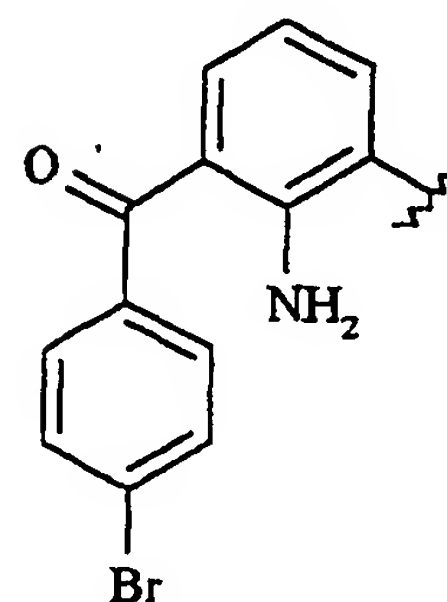
(XXXIII)



(XXXVI)



(XXXVII)



(XII)

wherein the meanings are the following:

- when R_{1a} is as defined in formula (IV), Ketoprofen residue: R_{III1} is H, SR_{III2} wherein R_{III2} contains from 1 to 4 carbon atoms, linear or branched when possible; R_{III2} is H, hydroxy;
- when R_{1a} is as defined in formula (XXI), carprofen residue: R_{XII0} is H, linear or branched when possible alkyl from 1 to 6 carbon atoms, C_1 - C_6 alkoxy carbonyl linked to a C_1 - C_6 alkyl, C_1 - C_6 carboxyalkyl, C_1 - C_6 alkanoyl, optionally substituted

with halogens, benzyl or halobenzyl, benzoyl or halobenzoyl;

R_{xx1} is H, halogen, hydroxy, CN, C_1-C_6 alkyl optionally containing OH groups, C_1-C_6 alkoxy, acetyl, benzyloxy, SR_{xx12} wherein R_{xx12} is C_1-C_6 alkyl; C_1-C_3 perfluoroalkyl; C_1-C_6 carboxyalkyl optionally containing OH groups, NO_2 , amino; sulphamoyl, di-alkyl sulphamoyl with C_1-C_6 alkyl or difluoroalkyl-sulphonyl with C_1-C_3 alkyl;

R_{xx11} is halogen, CN, C_1-C_6 alkyl containing one or more OH groups, C_1-C_6 alkoxy, acetyl, acetamido, benzyloxy, SR_{xx13} being R_{xx13} as above defined, C_1-C_3 perfluoroalkyl, hydroxy, C_1-C_6 carboxyalkyl, NO_2 , amino, mono- or di-alkyl-amino C_1-C_6 ; sulphamoyl, di-alkyl sulphamoyl C_1-C_6 , or di-fluoroalkylsulphamoyl as above defined; or R_{xx1} together with R_{xx11} is an alkylen dioxy C_1-C_6 ;

- when R_{1a} is as defined in formula (XXXV) tiaprofenic acid residue:

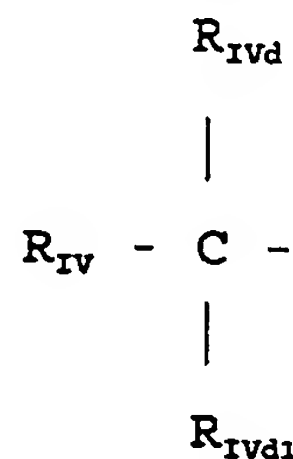
Ar is phenyl, hydroxyphenyl optionally mono or polysubstituted with halogen, alkanoyl and alkoxy C_1-C_6 , trialkyl C_1-C_6 , preferably C_1-C_3 , cyclopentyl, cyclohexyl, cycloheptyl, heteroaryl, preferably tienyl, furyl optionally containing OH, pyridyl;

- when R_{1a} is as defined in formula (II), suprofen residue, wherein R_{3a} is H, R_{2a} is methyl and $X = O$;
- when R_{1a} is as defined in formula (VI), R is the residue of indoprofen when $R_{2a} = H$ and $R_{3a} = CH_3$; of indobufen when R_{2a} is equal to H and $R_{3a} = C_2H_5$; $X = O$;
- when R_{1a} is as defined in formula (VIII), R is the etodolac residue when $R_{2a} = R_{3a} = H$ and $X = O$;
- when R_{1a} is as defined in formula (VII), R is the fenoprofen residue when $R_{3a} = H$, $R_{2a} = CH_3$ and $X = O$;
- when R_{1a} is as defined in formula (III), R is the fenbufen residue when $R_{2a} = R_{3a} = H$ and $X = O$;
- when R_{1a} is as defined in formula (IX), R is the flurbiprofen residue when $R_{3a} = H$, $R_{2a} = CH_3$, $X = O$;
- when R_{1a} is as defined in formula (X) R is the tolmetin residue when $R_{2a} = R_{3a} = H$, $X = O$;

in group IIID) R_{1a} corresponds to the following formulas:

- IIIa), when $R_{2a} = H$ and $R_{3a} = CH_3$, the pranoprofen residue is obtained: α -methyl-5H-[1]benzopyran-[2,3-b]pyridin-7-acetic acid; the preferred compound has $R_{2a} = H$, $R_{3a} = CH_3$, $u = 1$ and $X = O$;
- (XXX), when $R_{2a} = H$ and $R_{3a} = CH_3$, the bermoprofen residue is obtained: dibenz[b,f]oxepin-2-acetic acid;
- (XXXI), when $R_{2a} = H$ and $R_{3a} = CH_3$, R is the radical of the CS-670 compound: 2-[4-(2-oxo-1-cyclohexyliden methyl) phenyl]propionic acid;
- (XXXII), when $R_{2a} = R_{3a} = H$ the Pemedolac residue is obtained;
- (XXXIII), when $R_{2a} = R_{3a} = H$ the pirazolac residue is obtained: 4-(4-chlorophenyl)-1-(4-fluoro phenyl)-3-pyrazolic acid;
- (XXXVI), when $R_{2a} = H$, $R_{3a} = CH_3$, the zaltoprofen residue is obtained; when the residue is saturated with an hydroxyl or amino group, or with the carboxylic function the compounds are known as dibenzothiepine derivatives;
- (XXXVII), when $R_{2a} = R_{3a} = H$ the mofezolac residue is obtained: 3,4-di(p-methoxyphenyl)isoxazol-5-acetic acid;
- (XII), when $R_{2a} = R_{3a} = H$ the bromfenac residue is obtained: 2-amino-3-(4-bromobenzoyl)benzeneacetic acid;

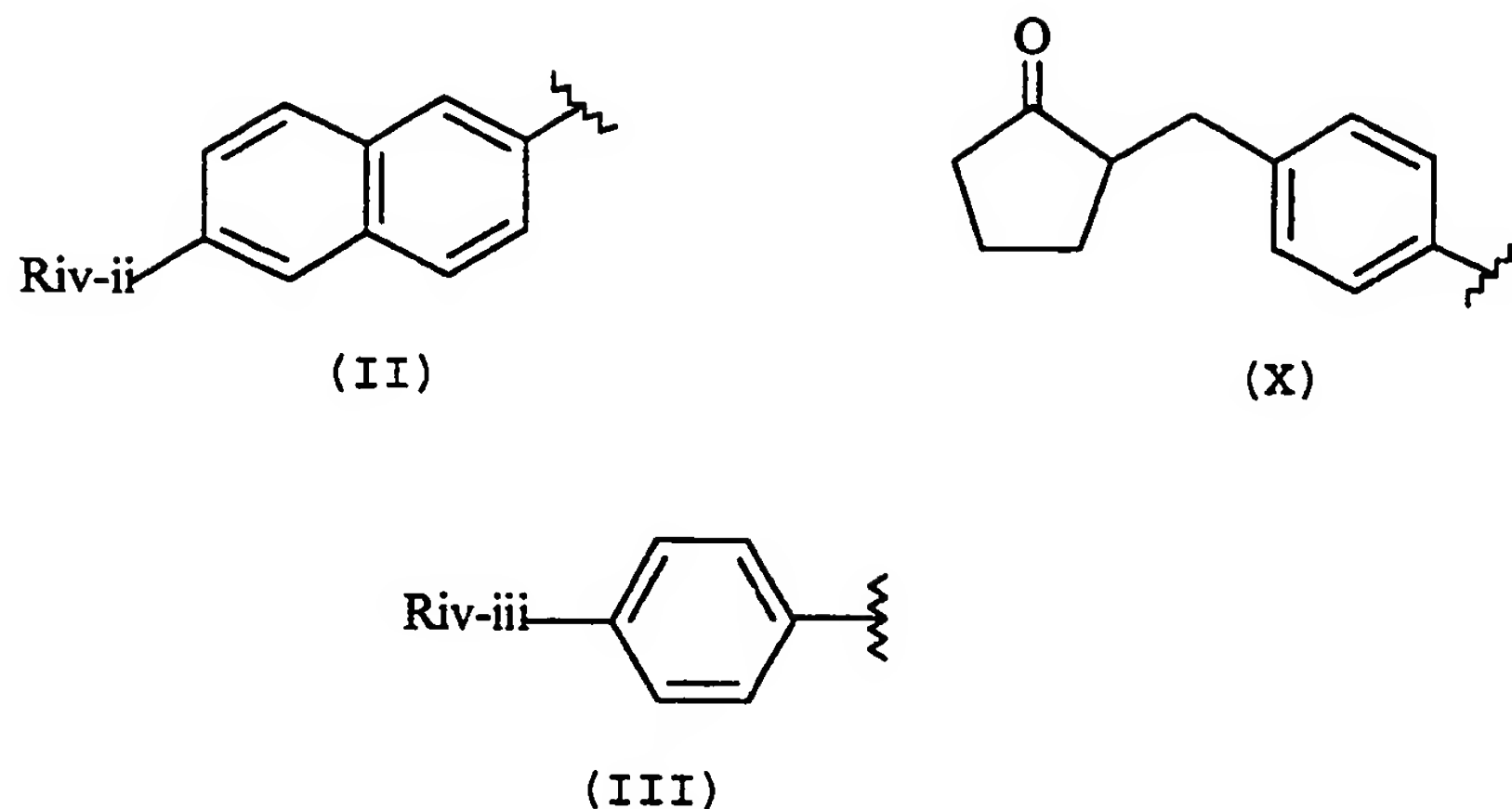
in group IV) wherein $t = 1$, $u = 1$, R is



wherein:

R_{IVd} and R_{IVd1} are at least one H and the other a linear or branched C_1 - C_6 , preferably C_1 and C_2 alkyl, or difluoroalkyl with the alkyl from 1 to 6 carbon atoms, C_1 is preferred, or R_{IVd} and R_{IVd1} form together a methylene group;

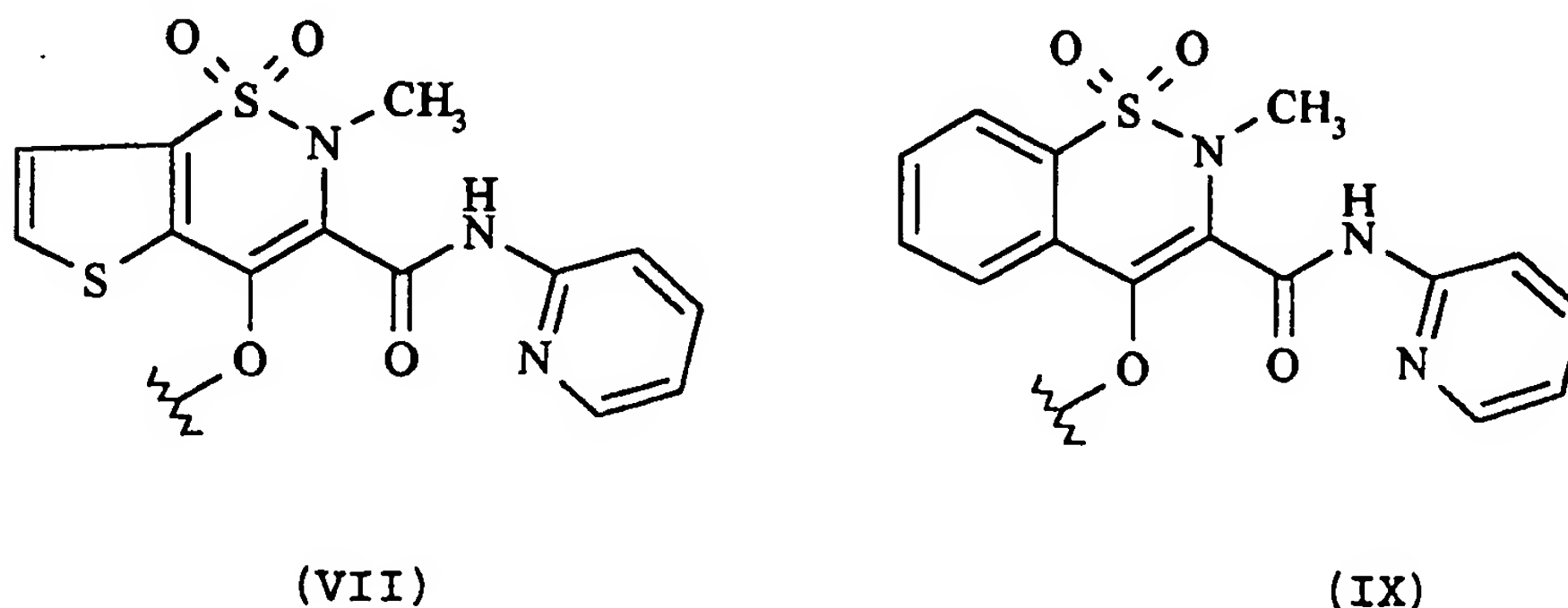
R_{IV} has the following meaning:

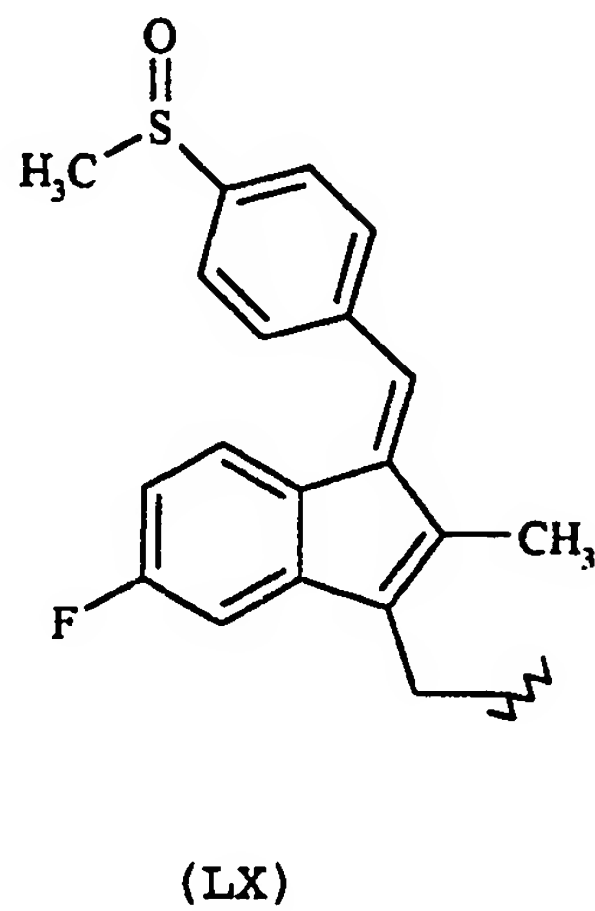
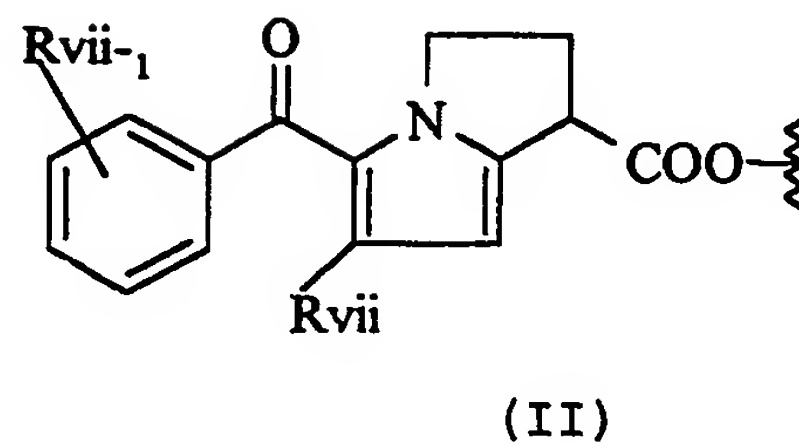
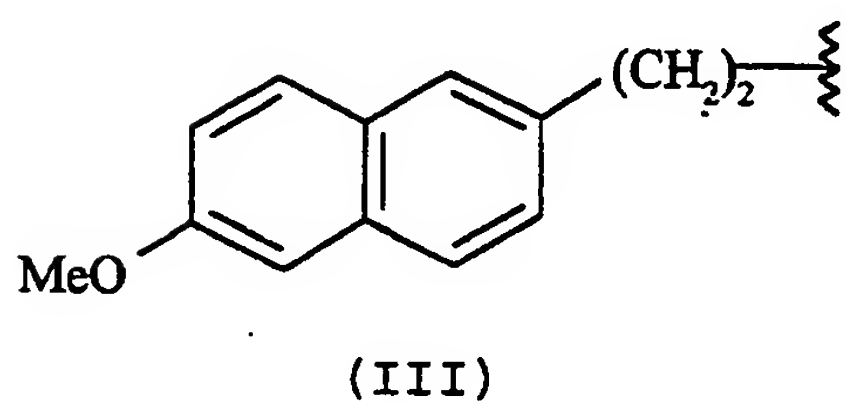
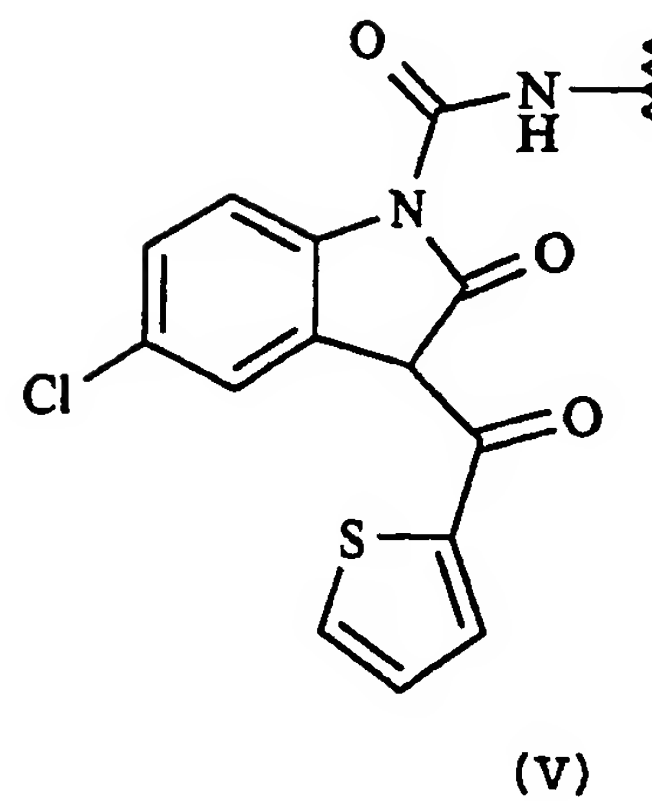
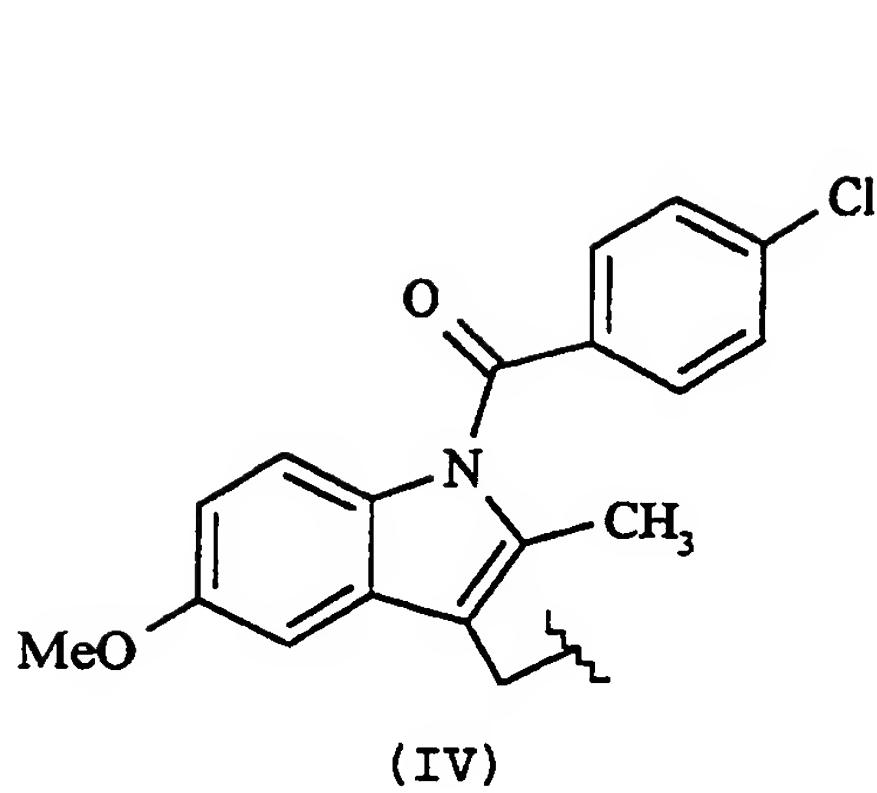


wherein the compounds of group IV) have the following meanings:

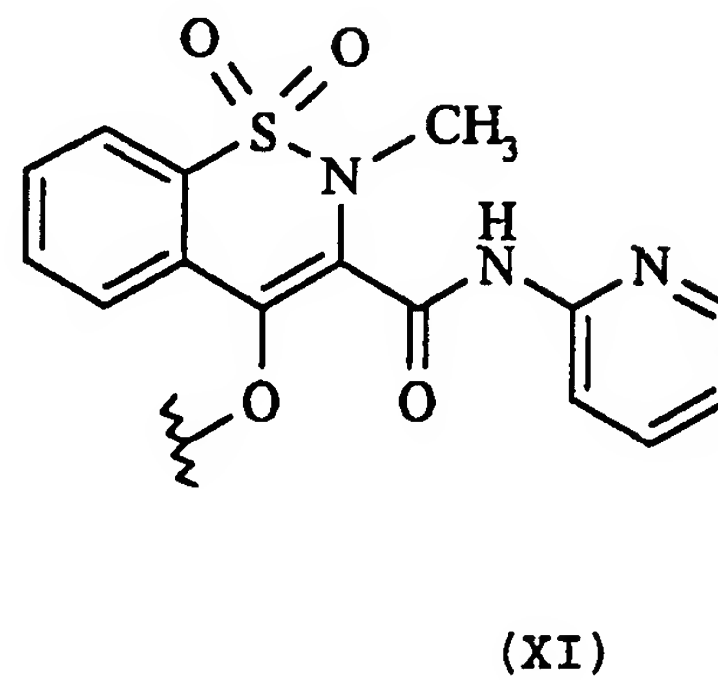
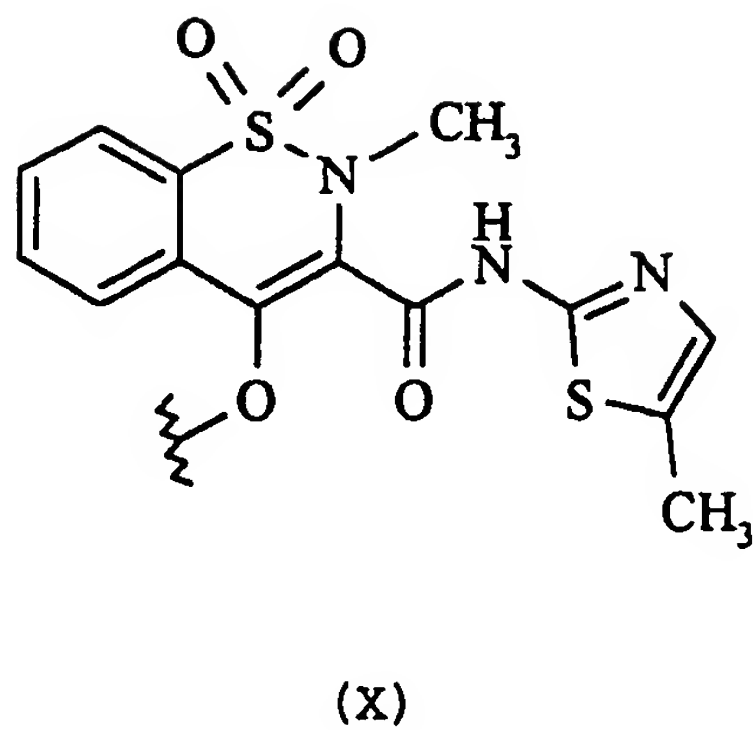
- in formula (II):
R_{IV-II} is C₁-C₆ alkyl, C₃-C₇ cycloalkyl, C₁-C₇ alkoxy-methyl, C₁-C₃ trifluoroalkyl, vinyl, ethynyl, halogen, C₁-C₆ alkoxy, difluoroalkoxy, with C₁-C₇ alkyl, C₁-C₇ alkoxy-methoxy, alkylthio methoxy with C₁-C₇ alkyl, alkyl methylthio with C₁-C₇ alkyl, cyano, difluoromethylthio, phenyl- or phenylalkyl substituted with C₁-C₆ alkyl.
- formula (X) loxoprofen residue;
- in formula (III):
R_{IV-III} is a C₂-C₅ alkyl, optionally branched when possible, C₂ and C₃ alkyloxy, allyloxy, phenoxy, phenylthio, cycloalkyl from 5 to 7 carbon atoms, optionally substituted in position 1 by a C₁-C₂ alkyl;

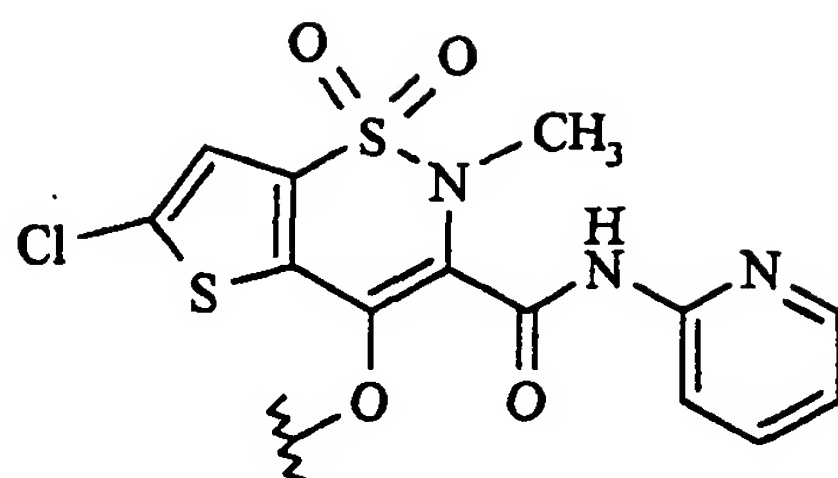
Group V)



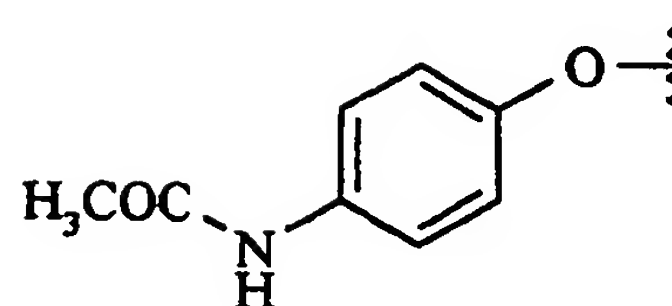


Group VB)

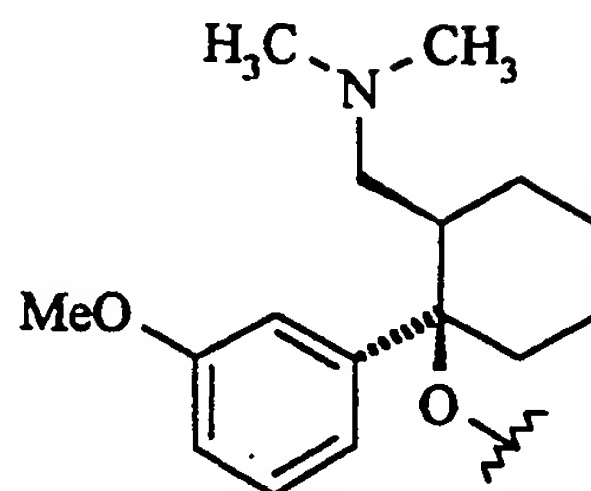




(XIII)



(XXXX)

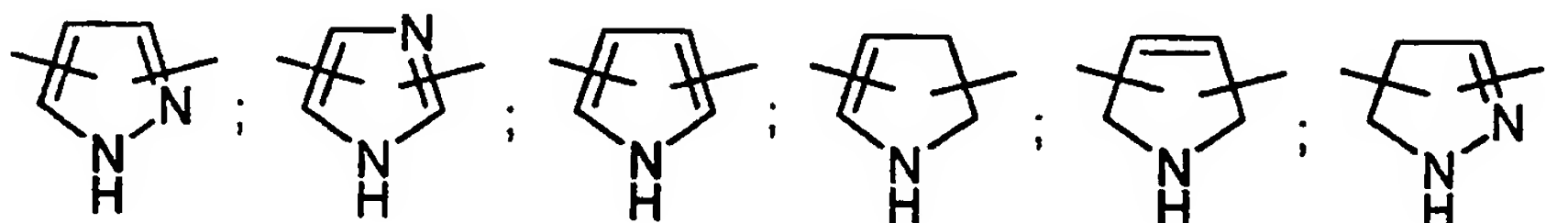


(XXXXI)

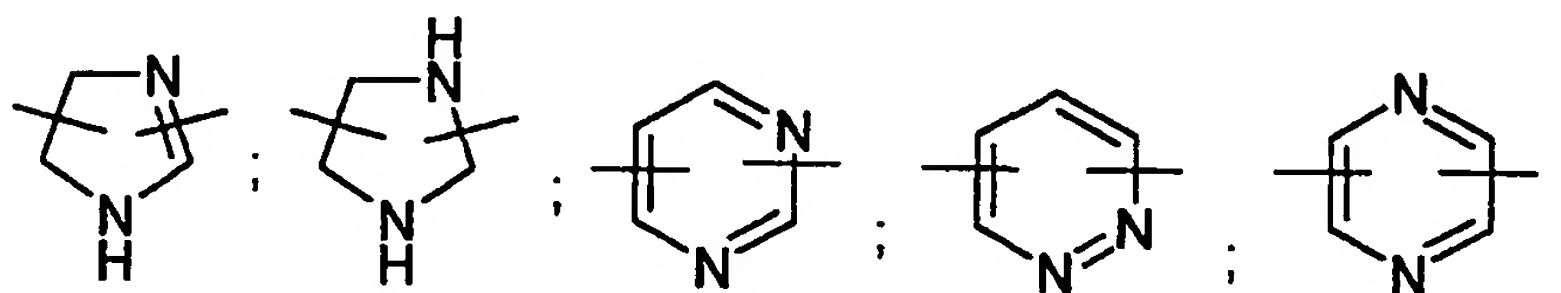
In group V) :

- when R is formula (II), R_{VII} is H or a linear or branched C_1 - C_4 alkyl;
 R_{VII-1} is R_{VII} , or a linear or branched C_1 - C_4 alkoxy;
 Cl, F, Br; the position of R_{VII-1} being ortho, or meta, or para;
- when R is formula (V),
 of which the residue of the known tenidap has been indicated;
- When R is formula (V) $A = R$ and $t = 0$,
- when R is formula (VII), A is RCO, $t = 1$ $u = 0$ or A is R and $t = 0$;
- when R is formula (IX), $A = R$ and $t = 0$, or $A = RCO$ with $t = 1$ and $u = 0$;
- when R is formula (III) $A = RCOO$, $t = 1$ and $u = 0$ or 1; or $t = 0$ and $A = R$;
- when R is formula (IV) $A = RCOO$, $t = 1$ and $u = 1$;
- when R is formula (LX) and in $(COX_u)_t$ $u = t = 1$ and X is oxygen, the precursor compound is sulindac;
- when R is formula (X) it is the meloxicam residue;
- when R is formula (XI) the residue is known as ampiroxicam when the termination is $-CH(CH_3)OCOC_2H_5$;

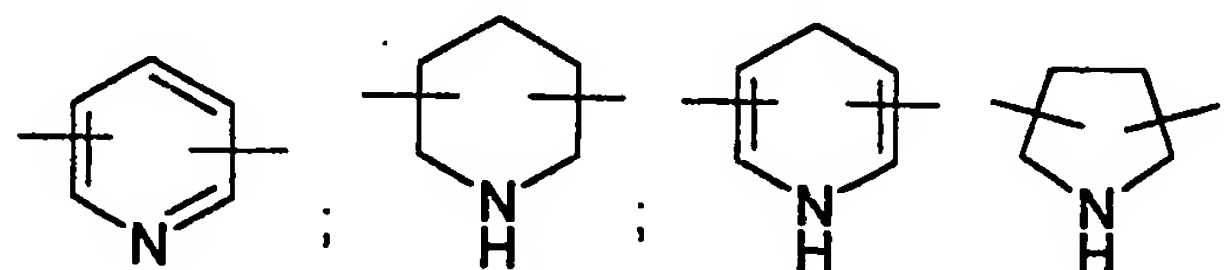
- when R is formula (XIII) and the valence is saturated with H, the residue derives from lornoxicam;
 - when R is formula (XXXX) and the valence is saturated with H the compound is known as paracetamol;
 - when R is formula (XXXXI) and the valence is saturated with H the compound is known as tramadol.
2. Use according to claim 1, wherein Y is selected from the following:



(Y1) (Y2) (Y3) (Y4) (Y5) (Y6)



(Y7) (Y8) (Y9) (Y10) (Y11)



(Y12) (Y13) (Y14) (Y15)

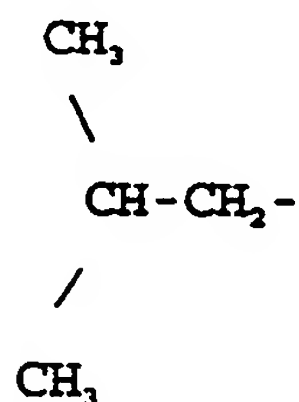
3. Use according to claim 2, wherein Y is Y12 (pyridyl) substituted in position 2 and 6.
4. Use according to claims 1-3, wherein in the compounds A) of formula $A-X_1-N(O)_z$, z is 2 and nIX and nIIX in formula (B) of X_1 are integers equal to 1 and R_{TIX} , $R_{TIX'}$, $R_{TIX''}$, $R_{TIX''}$ are equal to H.
5. Use according to claims 1-4, wherein in the compounds of formula A) $A-X_1-N(O)_z$, R, X, u and t of formula A = $R(COX_u)_t$, and Y in formula (B) of X_1 , take the following meanings:

- when R is selected from the group I), in the compounds of formula Ia) X is equal to O or NH, R₁ is acetoxy, preferably in ortho position with respect to -CO-, R₂ is hydrogen; in X₁ R_{TIIX} = R_{TIIX'} = R_{TIIX''} = R_{TIIX'''} = H, n_{IX} = n_{TIIX} = 1 and Y is an aromatic ring having 6 atoms, containing one nitrogen atom, said aromatic ring having the two free valences in position 2 and 6; in the compounds of formula Ib) R₃ = CH₃, nI = 0, X is equal to O, X₁ is as above defined for Ia); in this case Ib) is the residue of the acetylsalicylsalicylic acid;
- when R is selected in group II) in formula IIa R_{II1}, R_{II4} are hydrogen and R_{II2} and R_{II3} are chlorine in ortho position with respect to NH; R_{II5} and R_{II6} are H, X is equal to O, and X₁ is as above defined for the compounds of formula Ia);
- when R is selected in group III),
- when R_{1a} is as defined in formula (IV) R_{III1} and R_{III2} are H, R_{3a} is H, and R_{2a} is methyl, X = O;
- when R_{1a} is as defined in formula (XXI) R_{xx10} is H, the linking group is in position 2, R_{xx1} is H, R_{xx11} is chlorine and it is in para position with respect to nitrogen;
- when R_{1a} is as defined in formula (XXXV) Ar is phenyl, R_{3a} is H, R_{2a} is methyl and X is O; R_{3a} is H, R_{2a} is methyl and X is O;
- when R_{1a} is as defined in formula IIIa), R_{2a} = H, R_{3a} = CH₃, u = 1 and X = O;
- when R_{1a} is as defined in formula (XXX) R_{2a} = H, R_{3a} = CH₃, u = 1 and X = O;
- when R_{1a} is as defined in formula (XXXI), R_{2a} = H, R_{3a} = CH₃, u = 1 and X = O;
- when R_{1a} is as defined in formula (XXXII), R_{2a} = R_{3a} = H, u = 1 and X = O;
- when R_{1a} is as defined in formula (XXXIII), R_{2a} = R_{3a} = H, u = 1 and X = O;
- when R_{1a} is as defined in formula (XXXVI), R_{2a} = H, R_{3a} = CH₃, u = 1 and X = O;
- when R_{1a} is as defined in formula (XXXVII), R_{2a} = R_{3a} = H, t = 1 and X = O;

- when R_{1a} is as defined in formula (XII), $R_{2a} = R_{3a} = H$, $u = 1$, $t = 1$, $X = O$, $R_{2a} = R_{3a} = H$; or $t = 0$;

when R is selected in group IV),

- when R_{IV} is formula (II), $R_{IV-11} = CH_3O-$, $R_{IVd} = H$ and $R_{IVd1} = CH_3$, $X = O$ and X_1 is as above defined for Ia);
- when R_{IV} is formula (X), $R_{IVd} = H$, $R_{IVd1} = CH_3$, $X = O$ and X_1 is as above defined for Ia);
- when R_{IV} is formula (III), R_{IV-111} is



and $R_{IVd} = H$, R_{IVd1} is CH_3 , $X = O$ and X_1 is as above defined for Ia);

when R is selected in group V,

- when R is formula (II), R_{V11} and R_{V11-1} are H, and $A = R$;
- when R is formula (X), $A = RCO$, $t = 1$ and $u = 0$;
- when R is formula (XI), $A = RCO$, $t = 1$ and $u = 0$;
- when R is formula (XIII), $A = RCO$, $t = 1$ and $u = 0$;
- when R corresponds to formula (XXXX) or (XXXXI), $A = RCO$, $t = 1$ and $u = 0$.

Use according to claims 1-5, wherein the nitrate salts of the compounds inhibiting the phosphodiesterase are selected from the following: (C1) 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazol[4,3-d]-pyrimidin-5-yl)-phenyl]sulphonyl]-4-methyl-piperazine (Sildenafil), (C2) 2-(2-propyloxyphenyl)-8-azapurin-6-one (Zaprinast), (C3) 2,6-bis-(diethanolamino)-4,8-dipiperidine pyrimido [5,4-d]-pyrimidine (dipyridamol), (C4) 6-chloro-4-(1,3-dioxaindan-5-yl)methylamino-2(4-carboxy-1-piperidinyl)-quinazoline, (C5) N-(phenylmethyl)-1-ethyl-1H-pyrazol-[3,4-b]-quinolin-4-amine, (C6) 1-(2-chlorobenzyl)-3-isobutyryl-2-propyl-6-amino carbonyl-indol, (C7) 1-benzyl-6-chloro-2-[1-[3-(imidazol-1-yl)propyl]indol-5-yl-amino carbonyl] benzimidazol, (C8) 2-(1-imidazolyl)-5-(phenyl)-4-(1,3-dioxaindan-5-yl)methyl

aminopyrimidine, (C9) 6-ethynyl-4-(2-methoxyethyl) amino-2-(1-imidazolyl)quinazoline, (C10) 1-cyclopentyl-3-ethyl-6-(2-propoxyphenyl)pyrazol[3,4-d]pyrimidin-4-one, (C11) 1-cyclopentyl-3-ethyl-6-(4-methoxybenzyl)-pyrazol[3,4-d]-pyrimidin-4-one, (C12) 1,3-dimethyl-6-(2-propoxy-5-methansulphonamidophenyl)-1,5-dihydro pyrazol[3,4-d]-pyrimidin-4-one, (C13) (6R, 12aR)-2,3, 6,7,12, 12a-hexahydro-2-methyl-6-(1,3-dioxan-5-yl)pyrazine [2',1':6,1] pyrido[3,4-b]indol-1,4-dione, (C14) 1-propyl-3-methyl-6-[2-propoxy-5-[(4'-methyl-1-pyrazinyl)sulphonamido] phenyl]-1,5-dihydropyrazol[3,4-d]pyrimidin-4-one, (C15) 3-(4-amino carbonyl-1-piperidinyl)-6-cyan-8-(3-chloro-4-methoxy-phthalazine, (C16) 2-(1-imidazolyl)-4-(1,3-dioxaindan-5-yl) methylamino-7,8-dihydro-5H-thiopyran[3,2-d]pyrimidine, (C17) 1-Cyclopentyl-3-ethyl-6-(3-ethoxypyrid-4-yl)-1H-pyrazolo [3,4-d]pyrimidin-4-one, (C18) 1-[3-[1-[(4-Fluorophenyl) methyl]-7,8-dihydro-8-oxo-1H-imidazo[4,5-g]quinazolin-6-yl]-4-propoxyphenyl] carboxamide.

7. Use according to claims 1-6, obtained by the pharmaceutical formulations containing one or more salts of classes A) and C).
8. Use according to claim 7, wherein said formulaions are administrable by oral and sublingual route.
9. Use according to claims 1-7 wherein said formulations are for topical use and comprise as active principles also the salts of compounds C) different from nitrates.
10. Use according to claim 9, wherein the organic anions of said salts of compounds C) different from nitrates are selected from oxalate, tartrate, maleate, succinate, citrate, glycinate, lysinate; and the inorganic ones are selected from chloride, sulphate, phosphate.
11. Use according to claims 9-10, wherein the formulations for topical use comprise an active principle amount in the range 0.5 and 10% by weight.

12/36

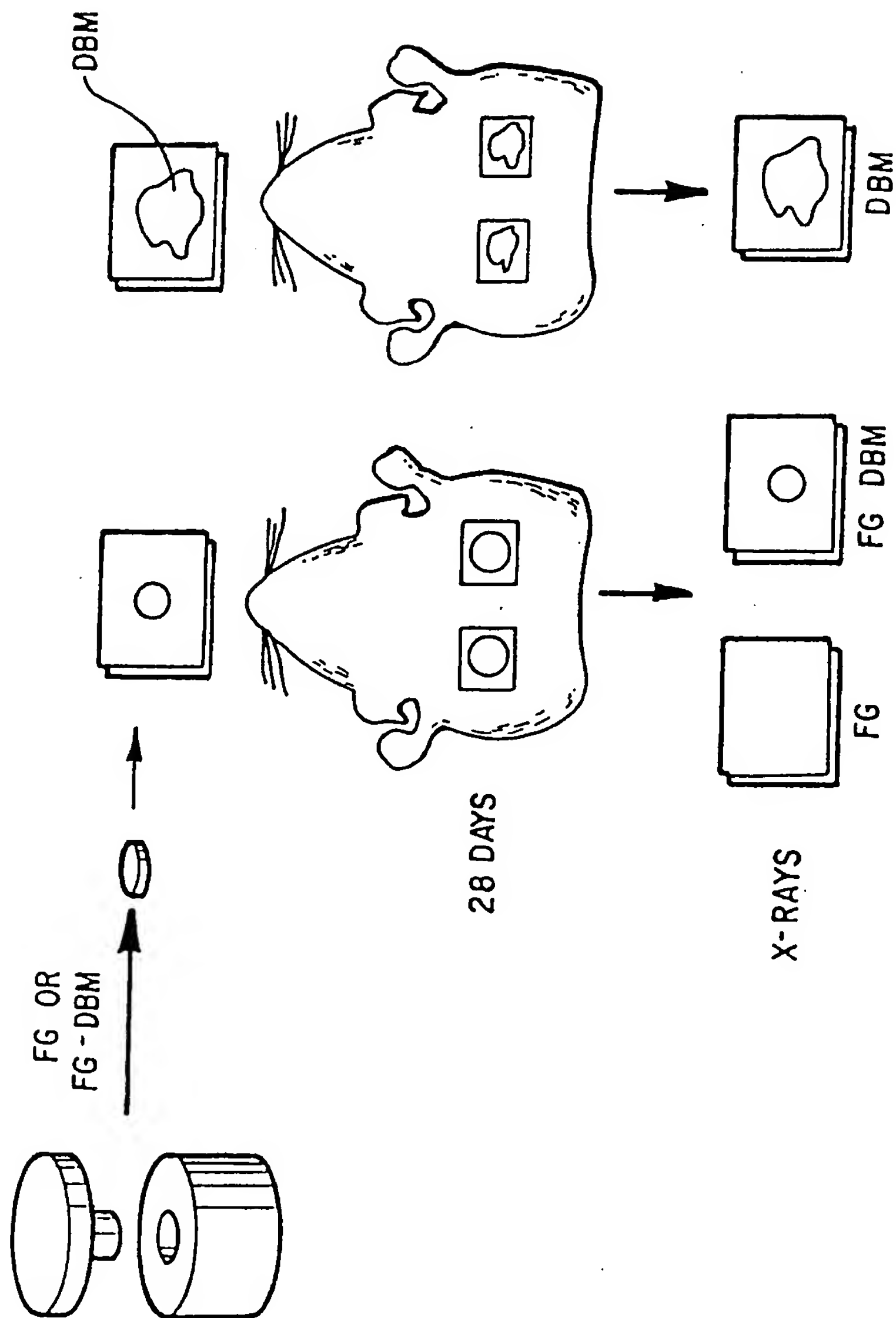


FIG. 15

13/36

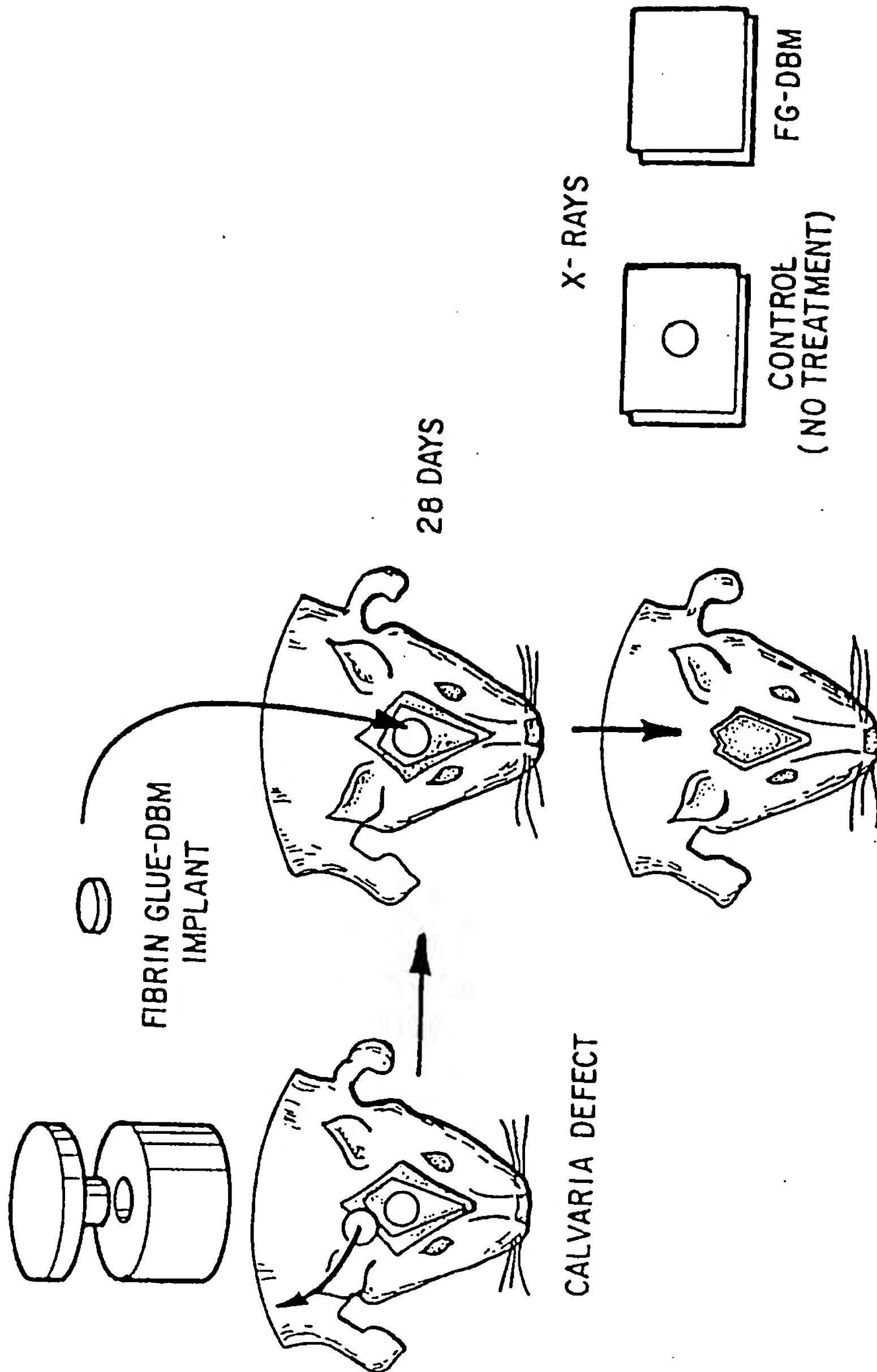


FIG. 16

14/36

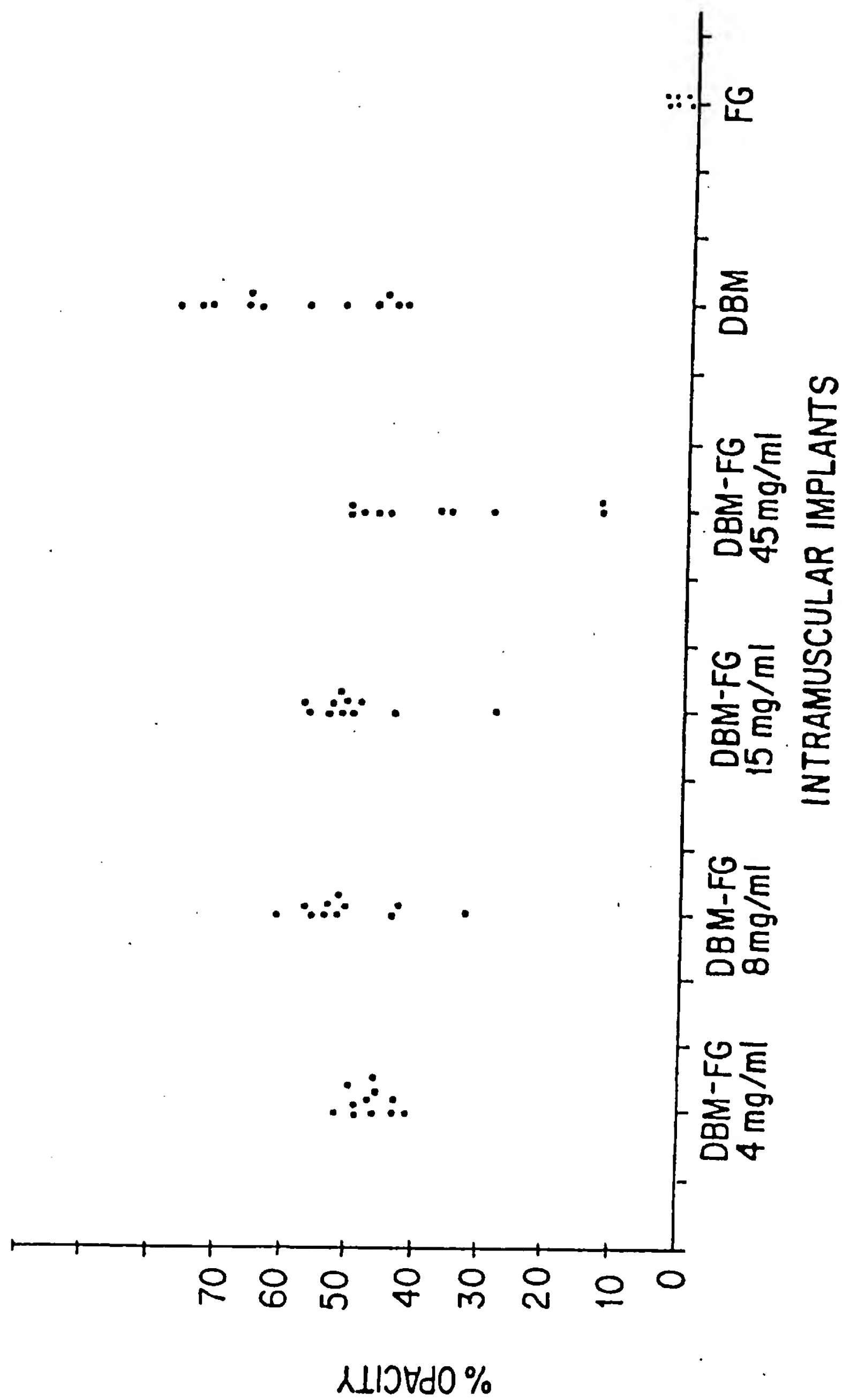


FIG. 17

15/36

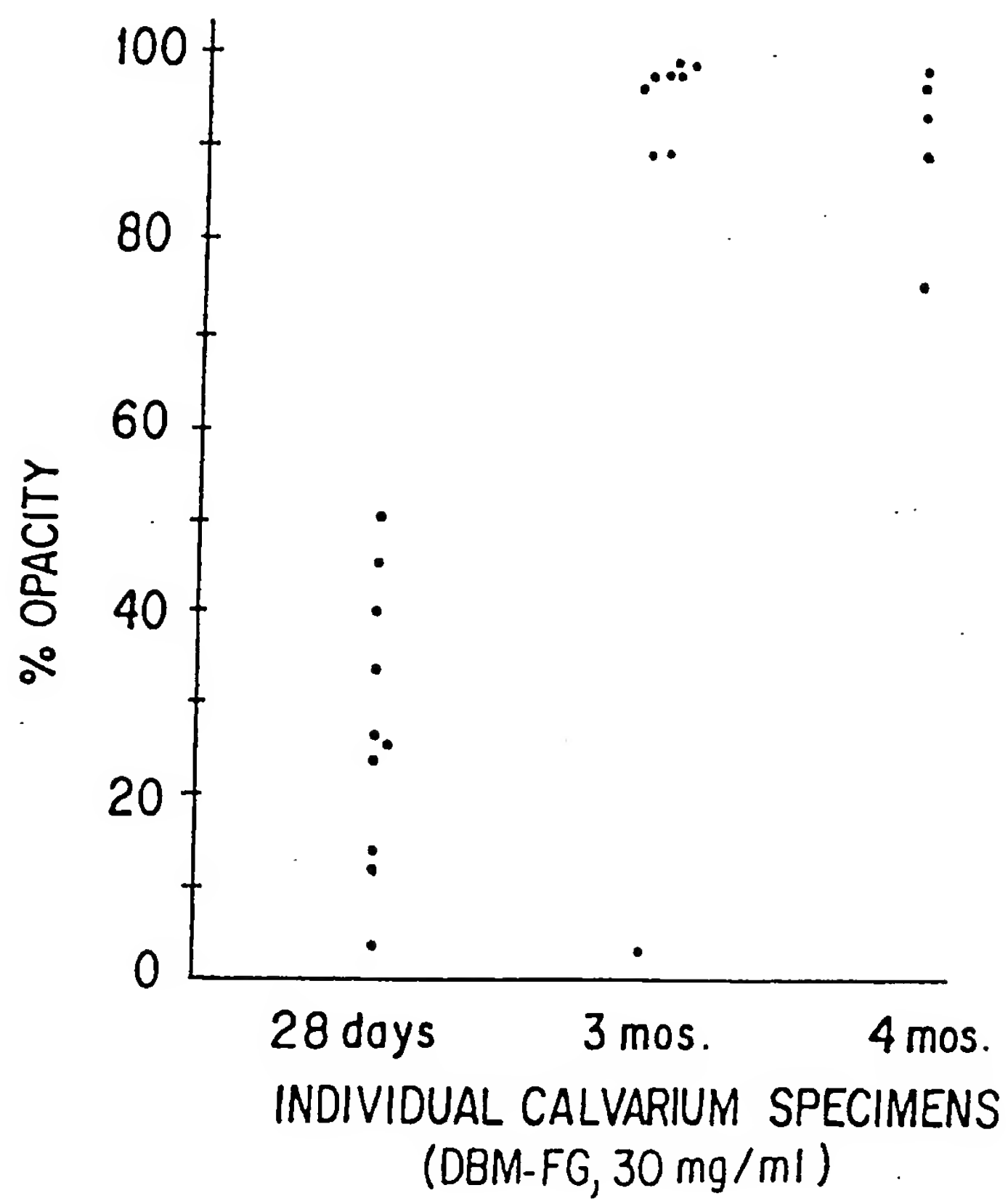


FIG. 18



FIG. 19A

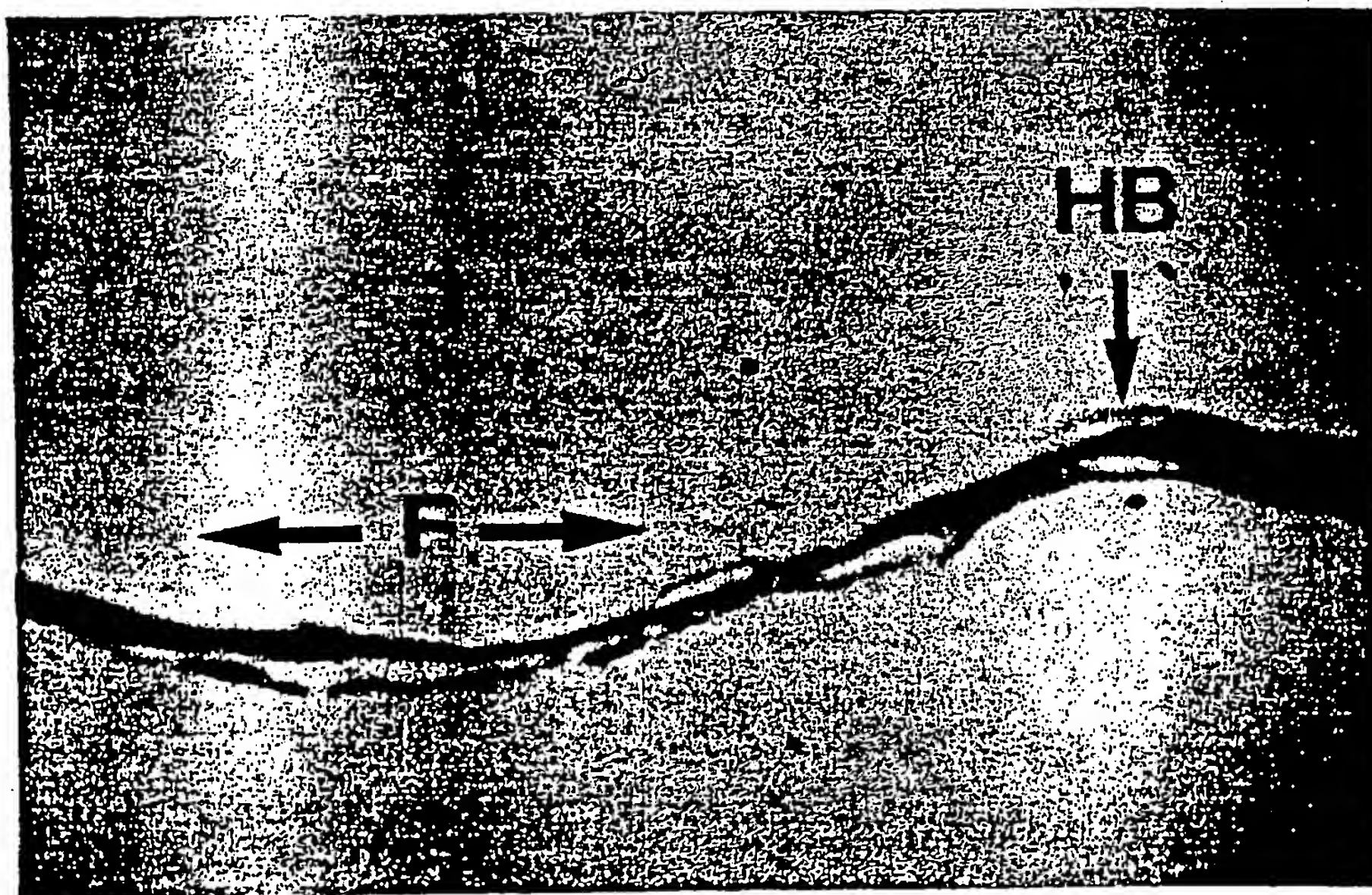


FIG. 19B

17/36

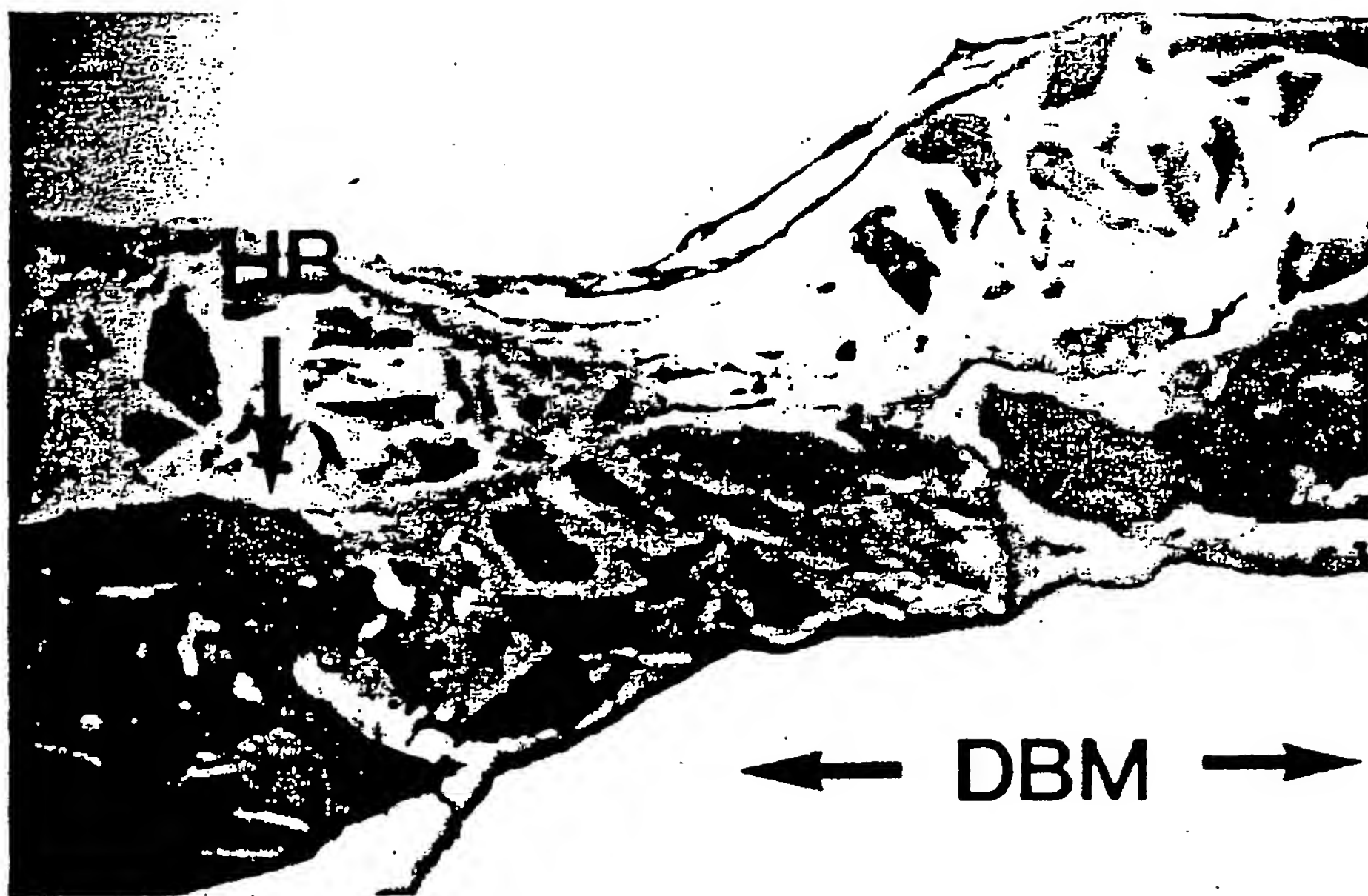


FIG.20



FIG.21



FIG.22

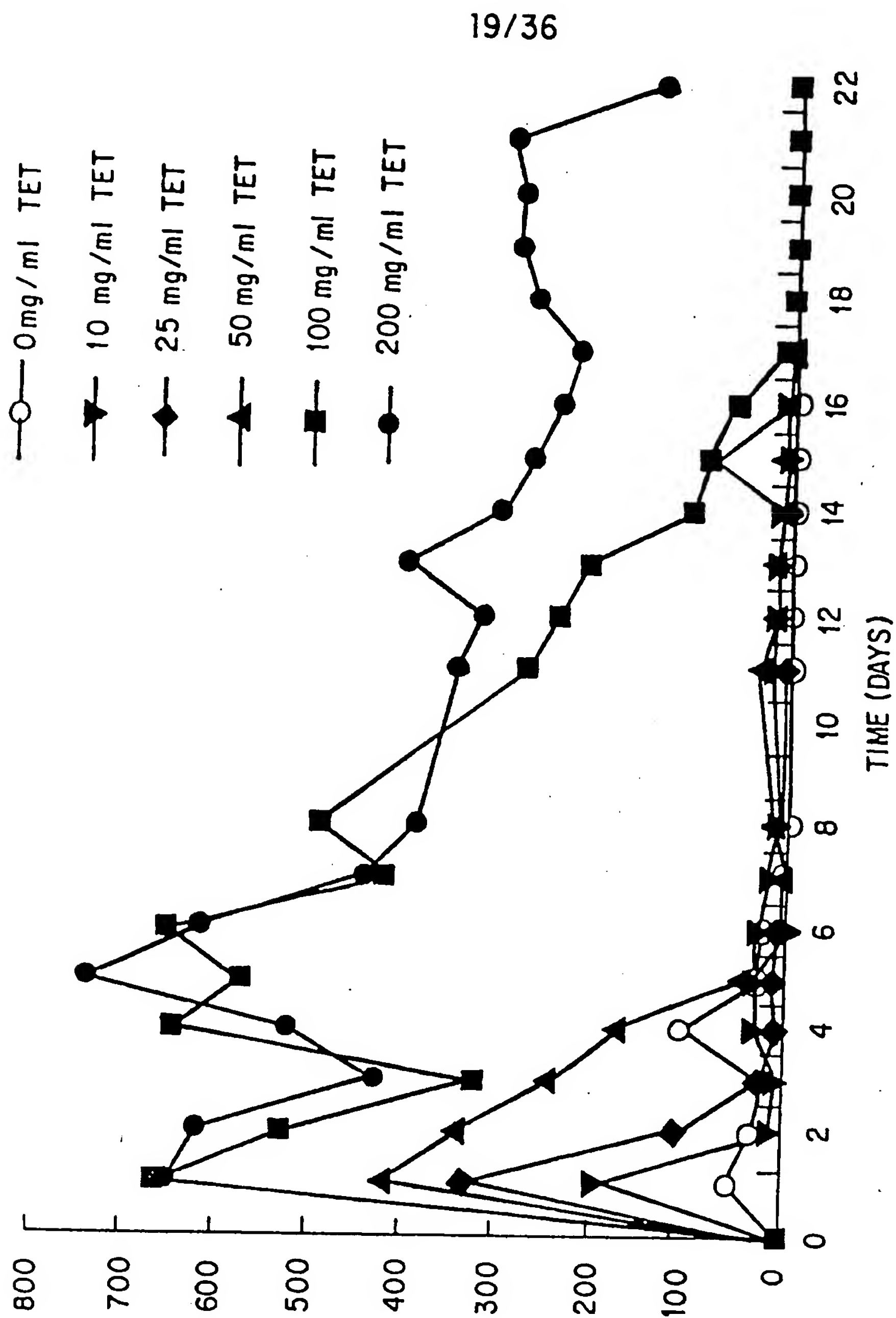


FIG. 23

20/36

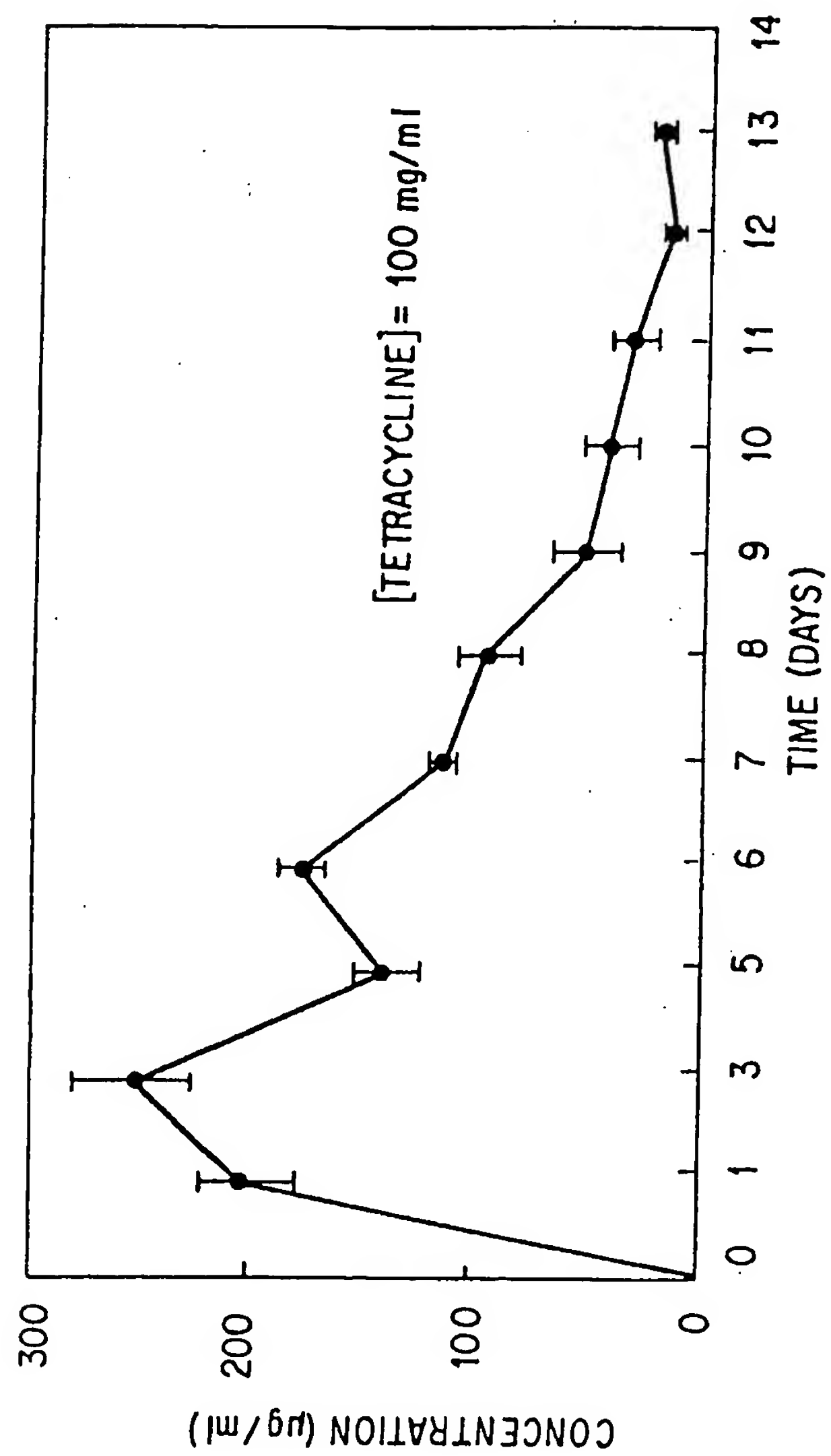


FIG. 24

21/36

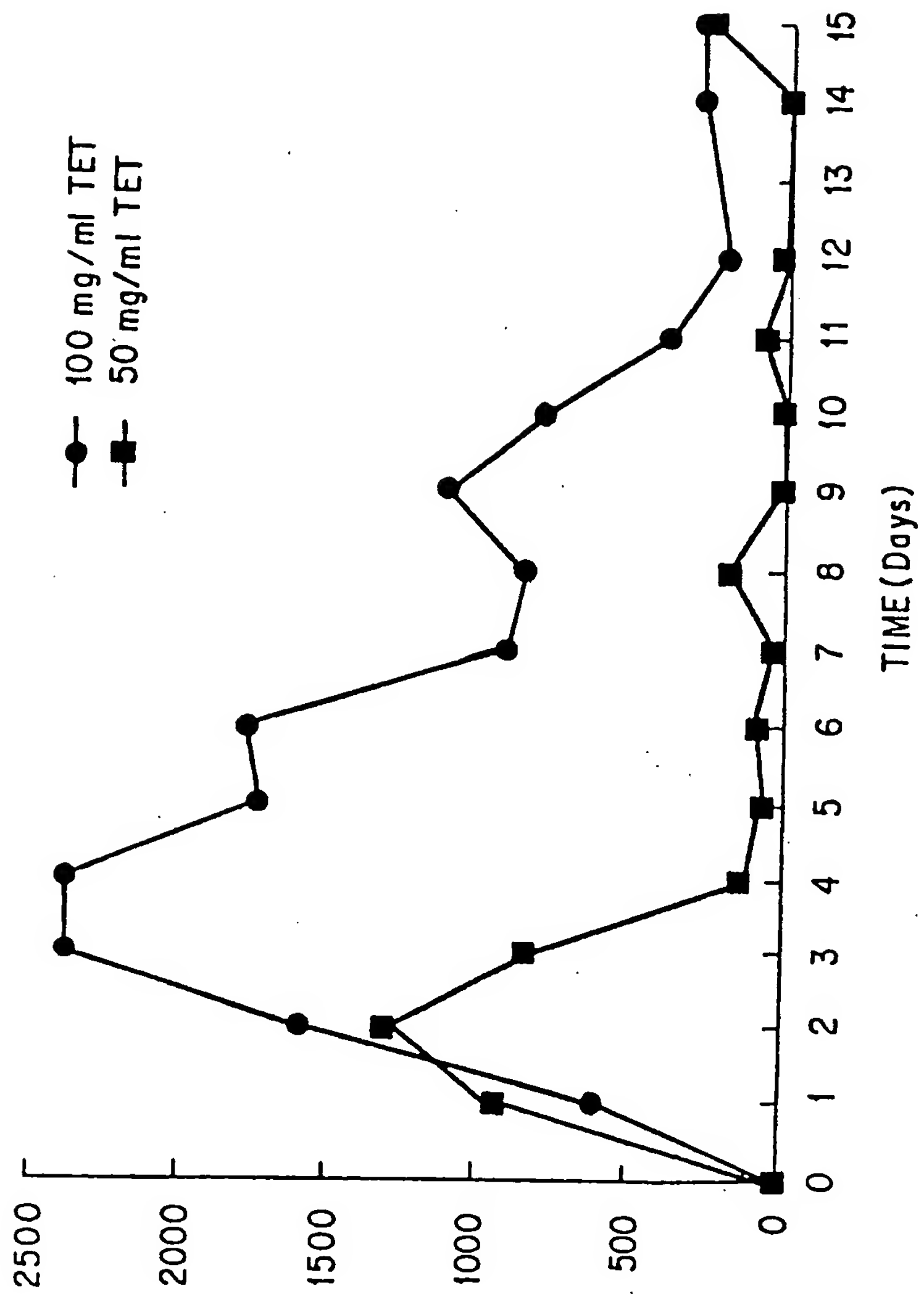


FIG. 25

22/36

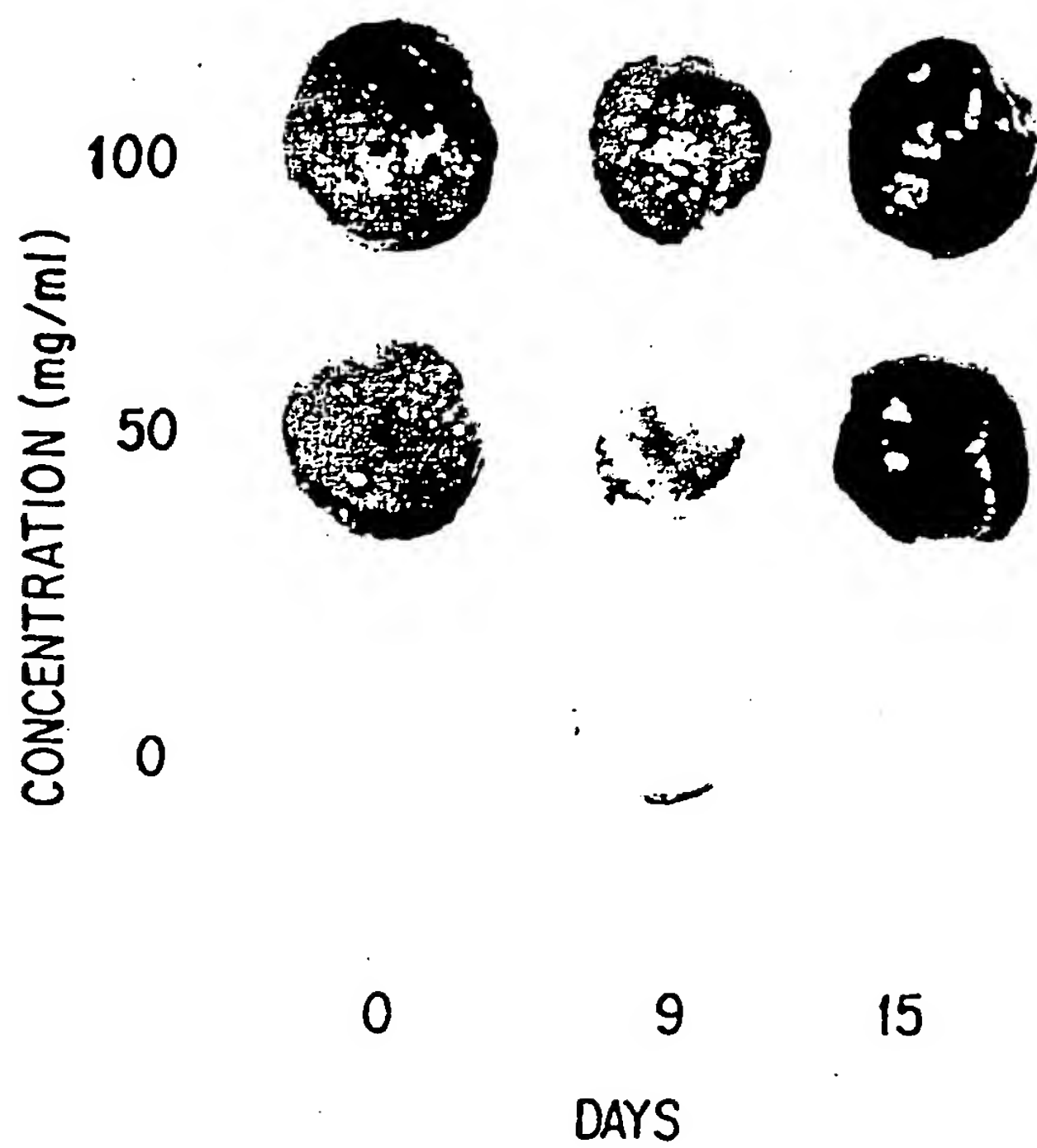
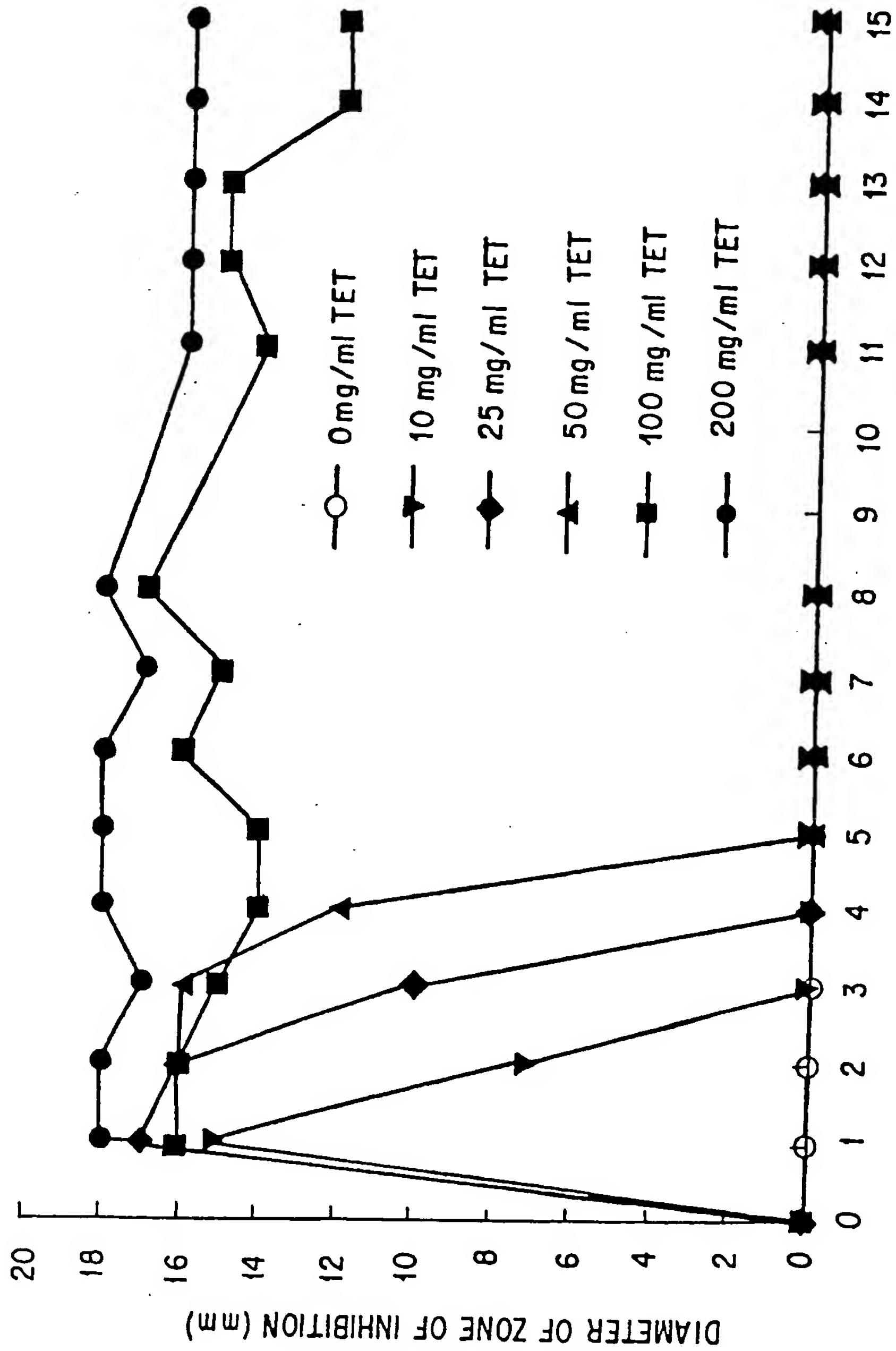


FIG.26

23/36



TIME (Days)

FIG.27

24/36

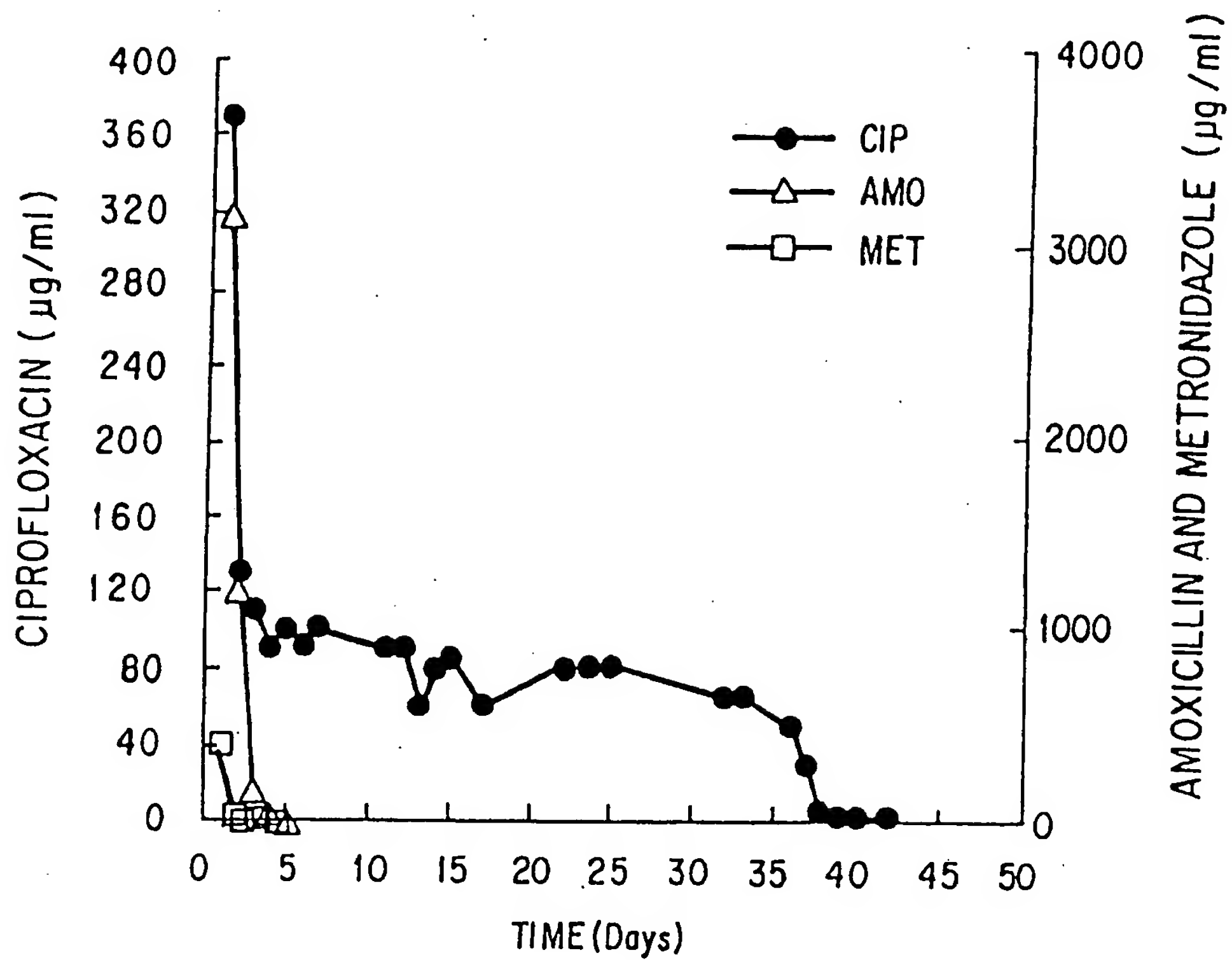


FIG. 28

25/36

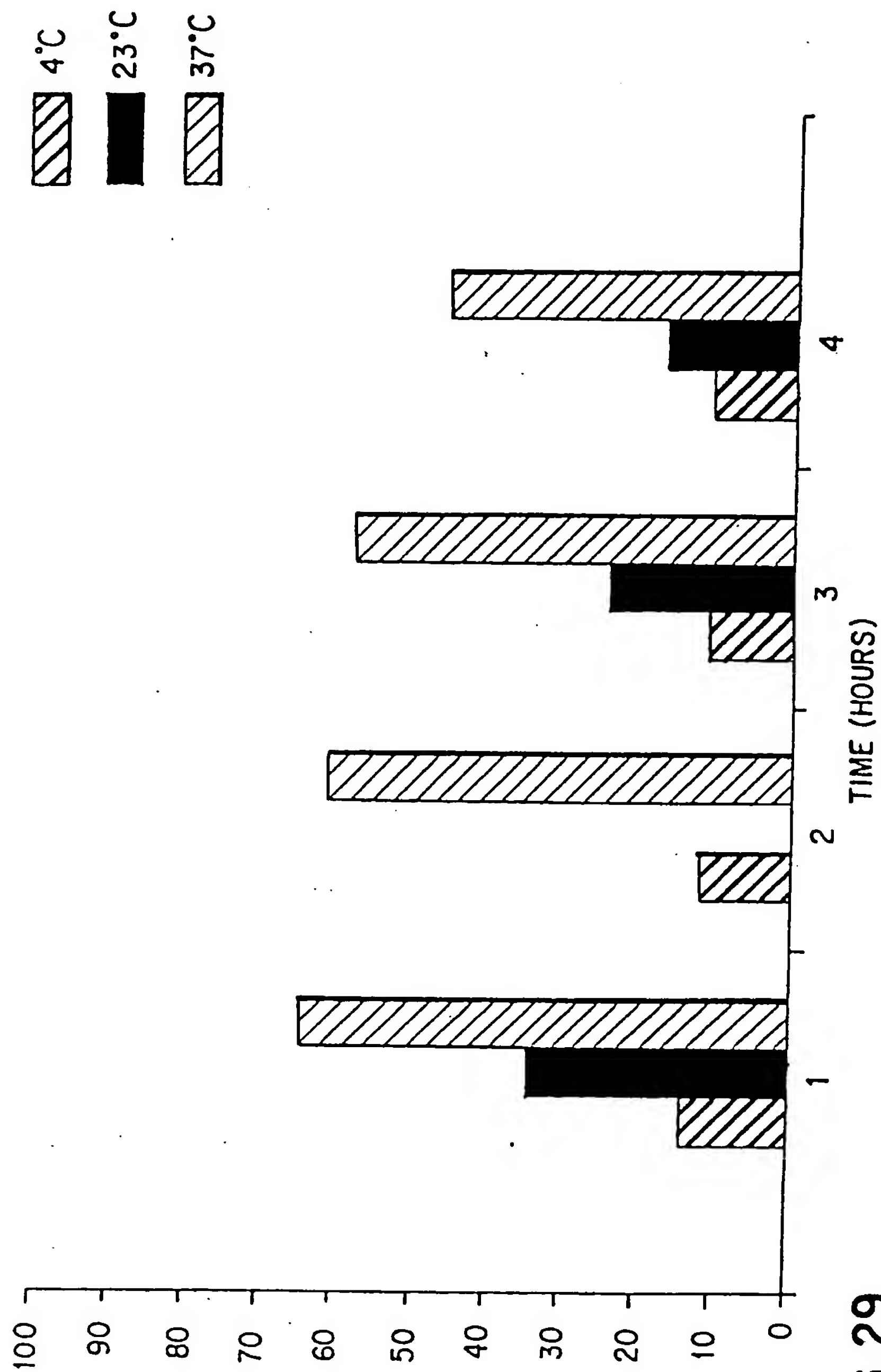


FIG. 29

26/36

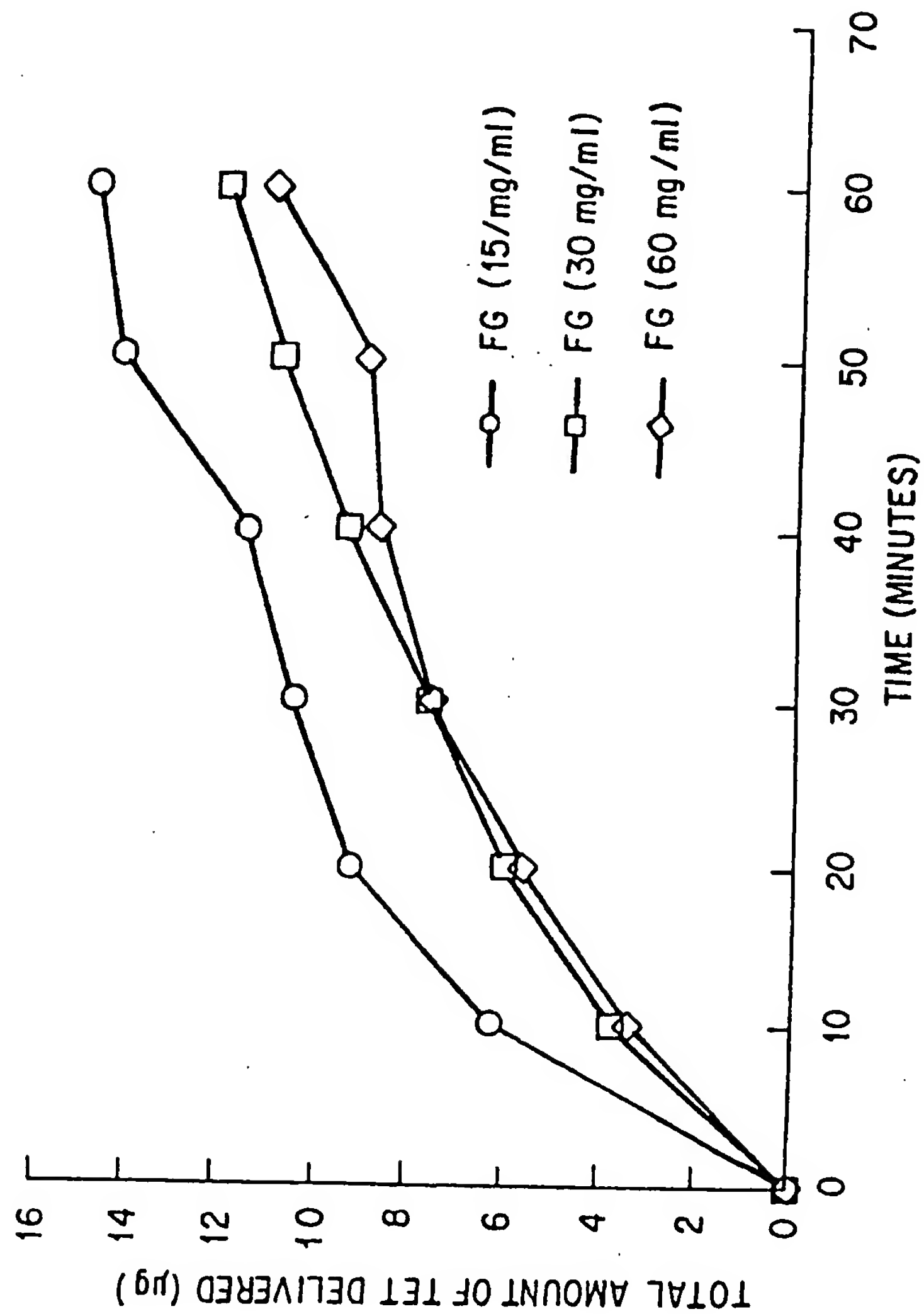


FIG. 30

27/36

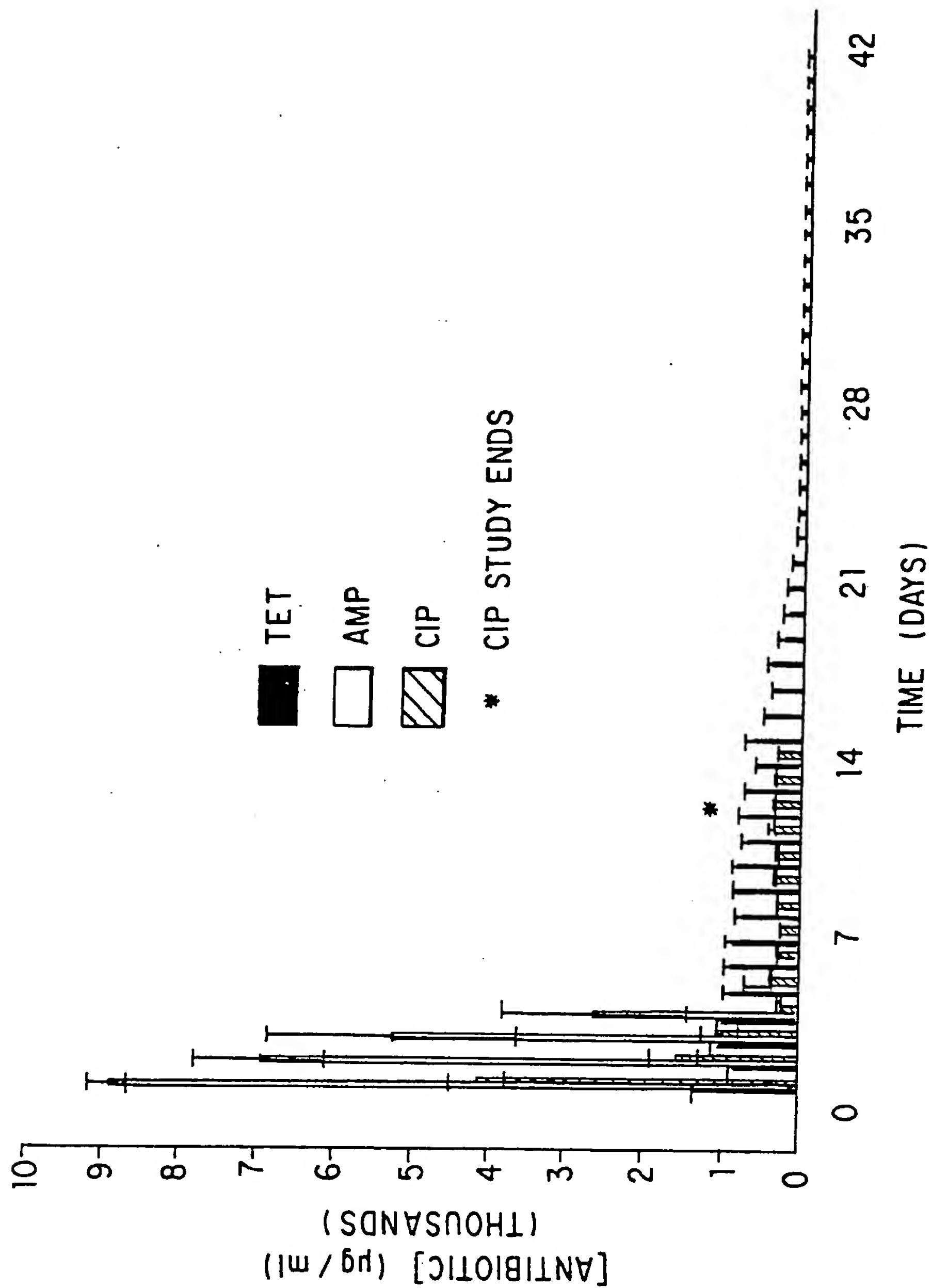


FIG. 31A

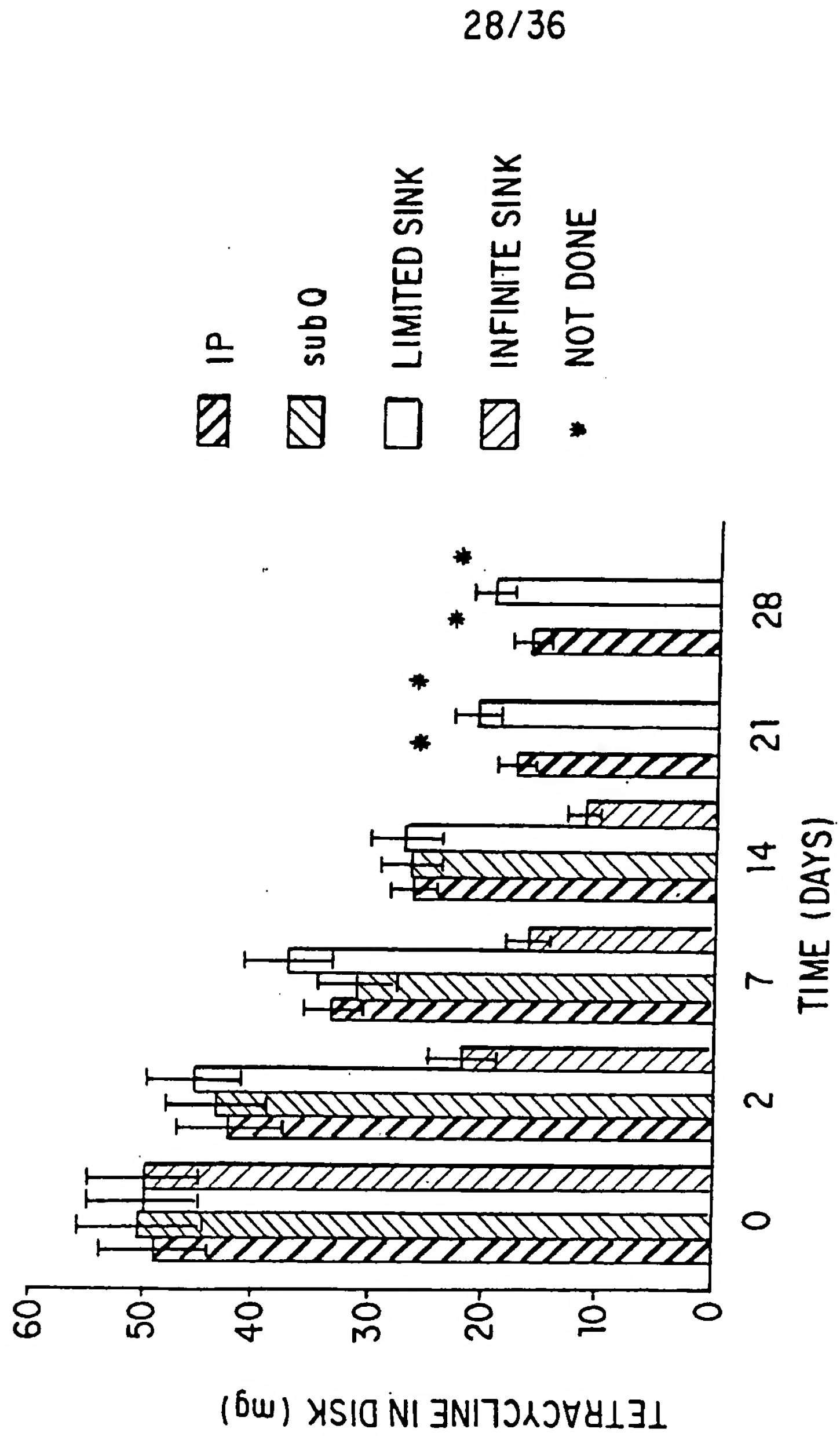


FIG. 31B

29/36

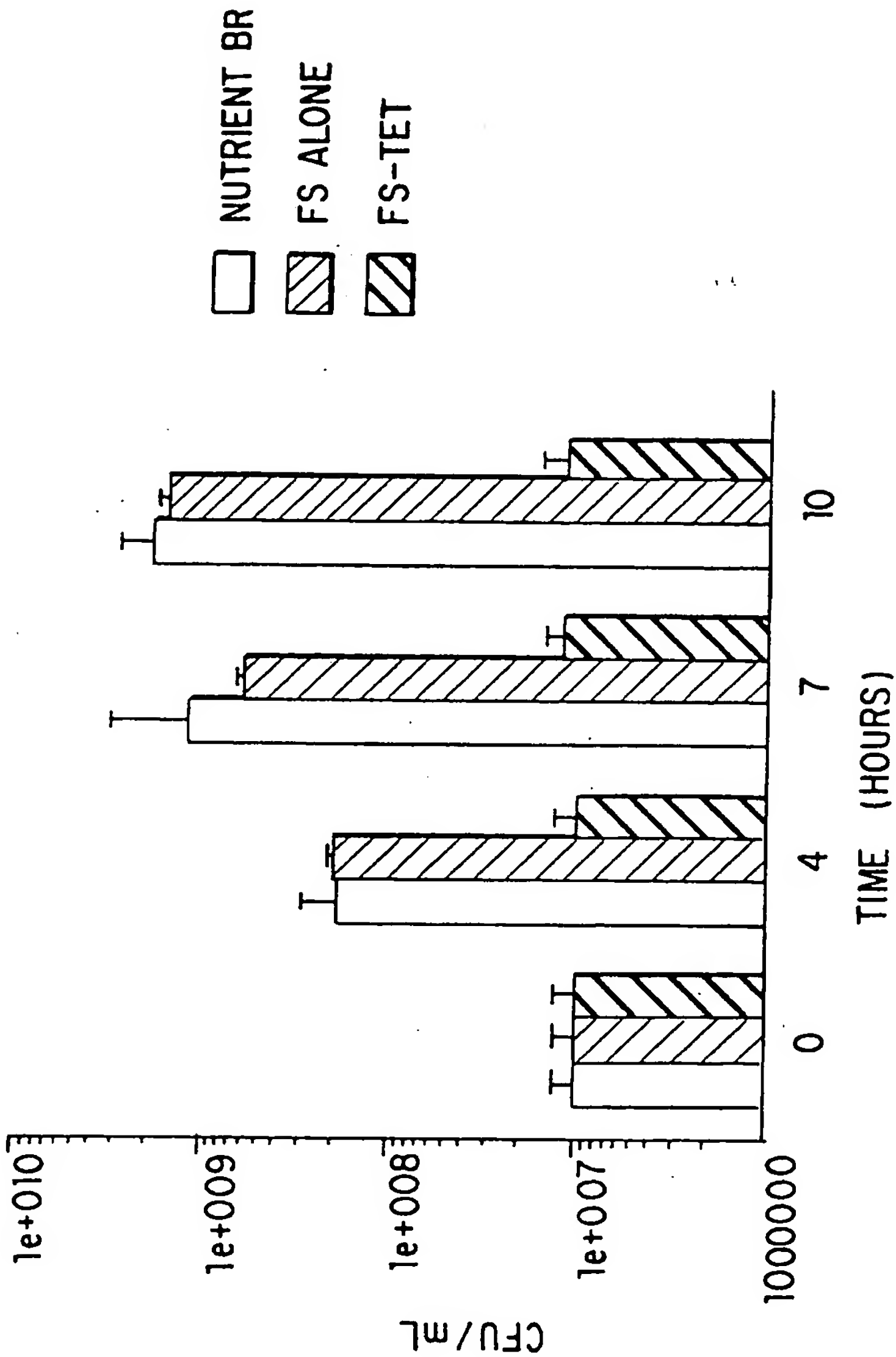


FIG. 31C

30/36

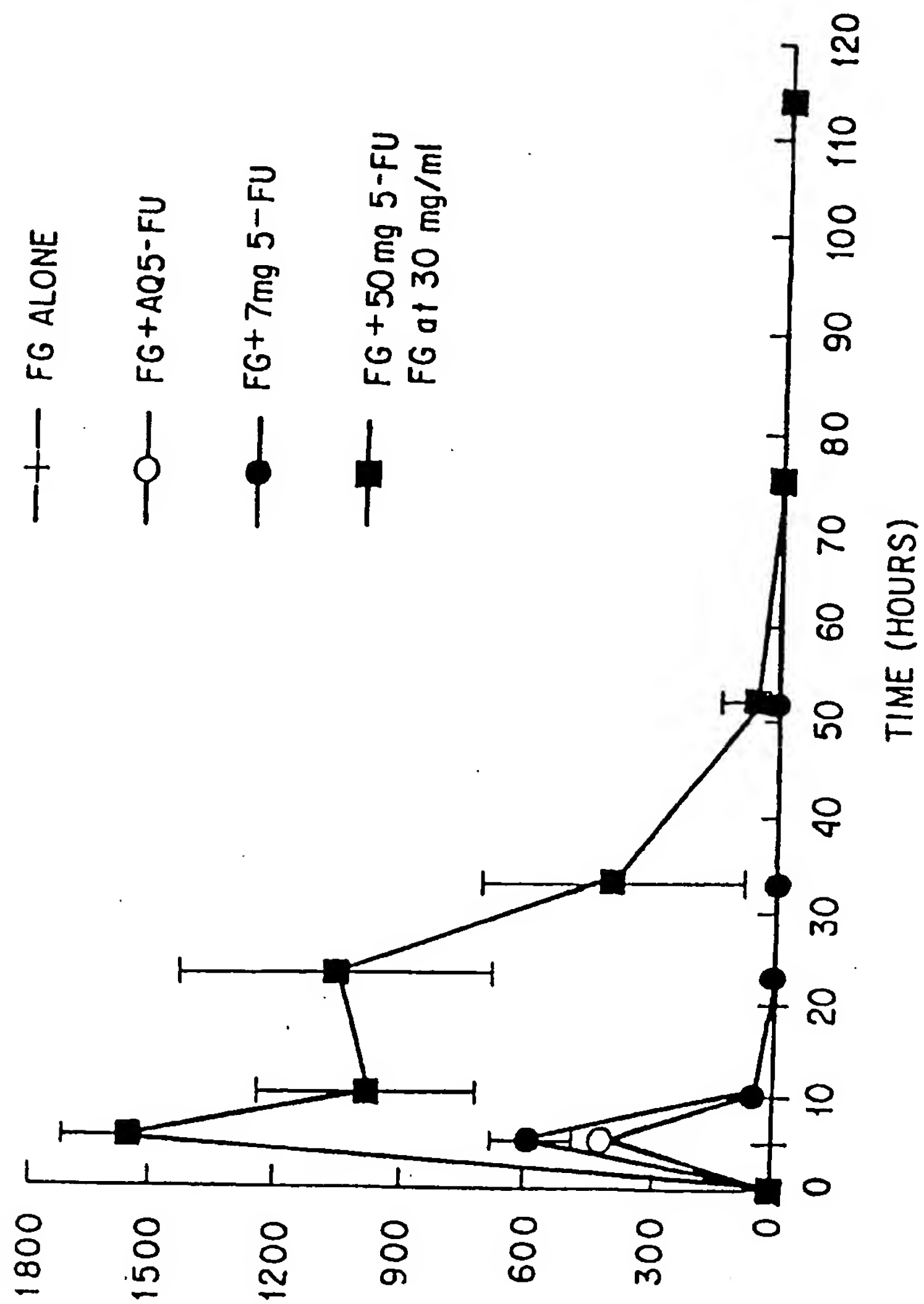
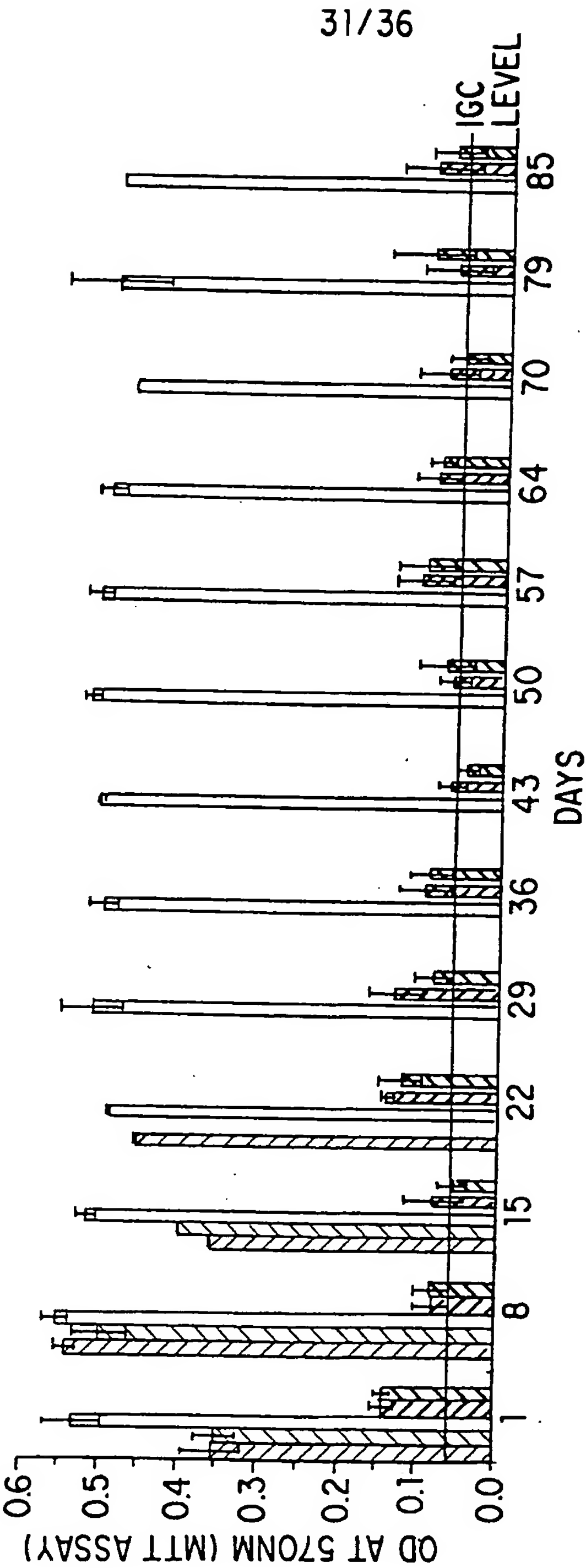
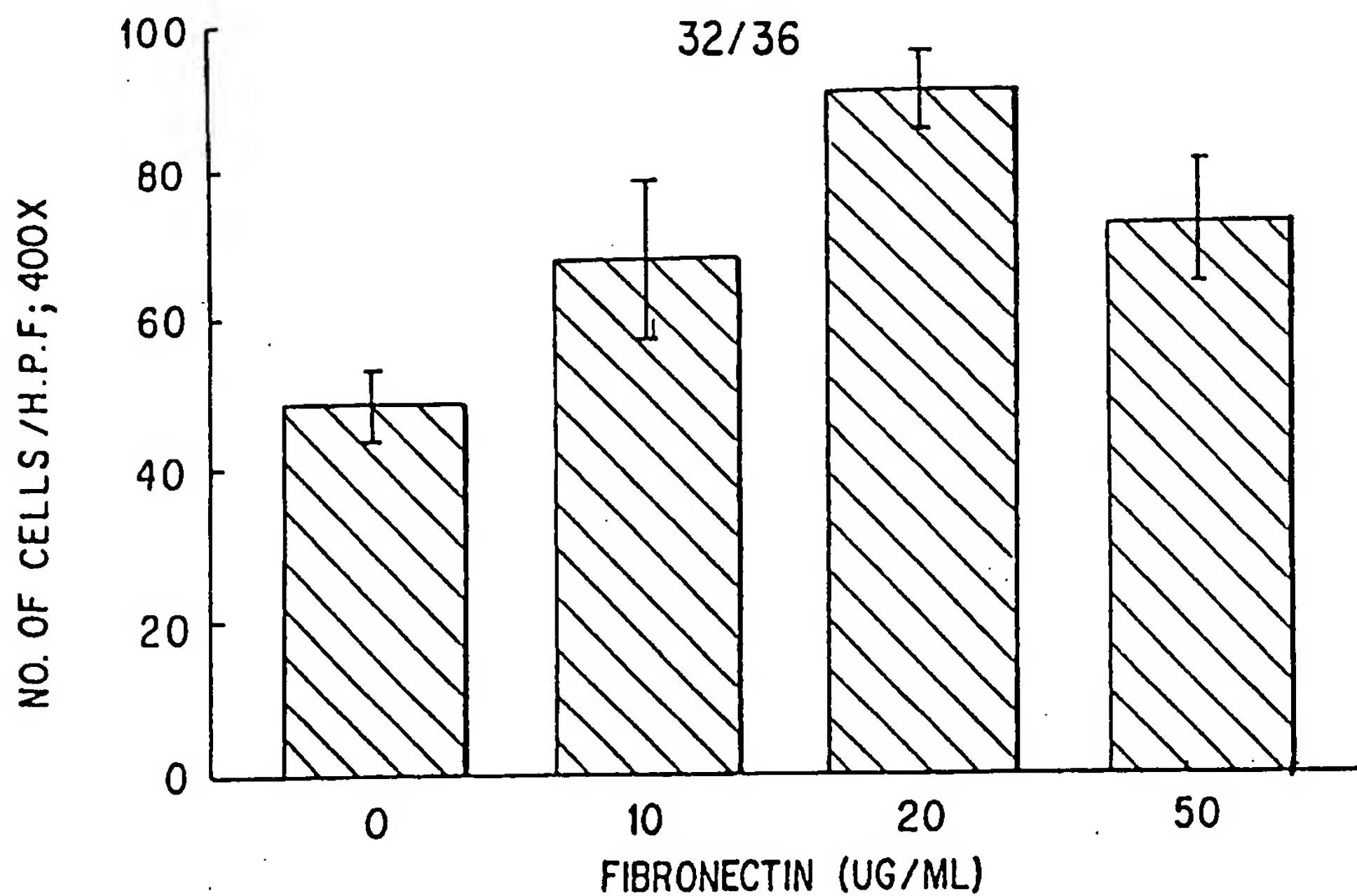
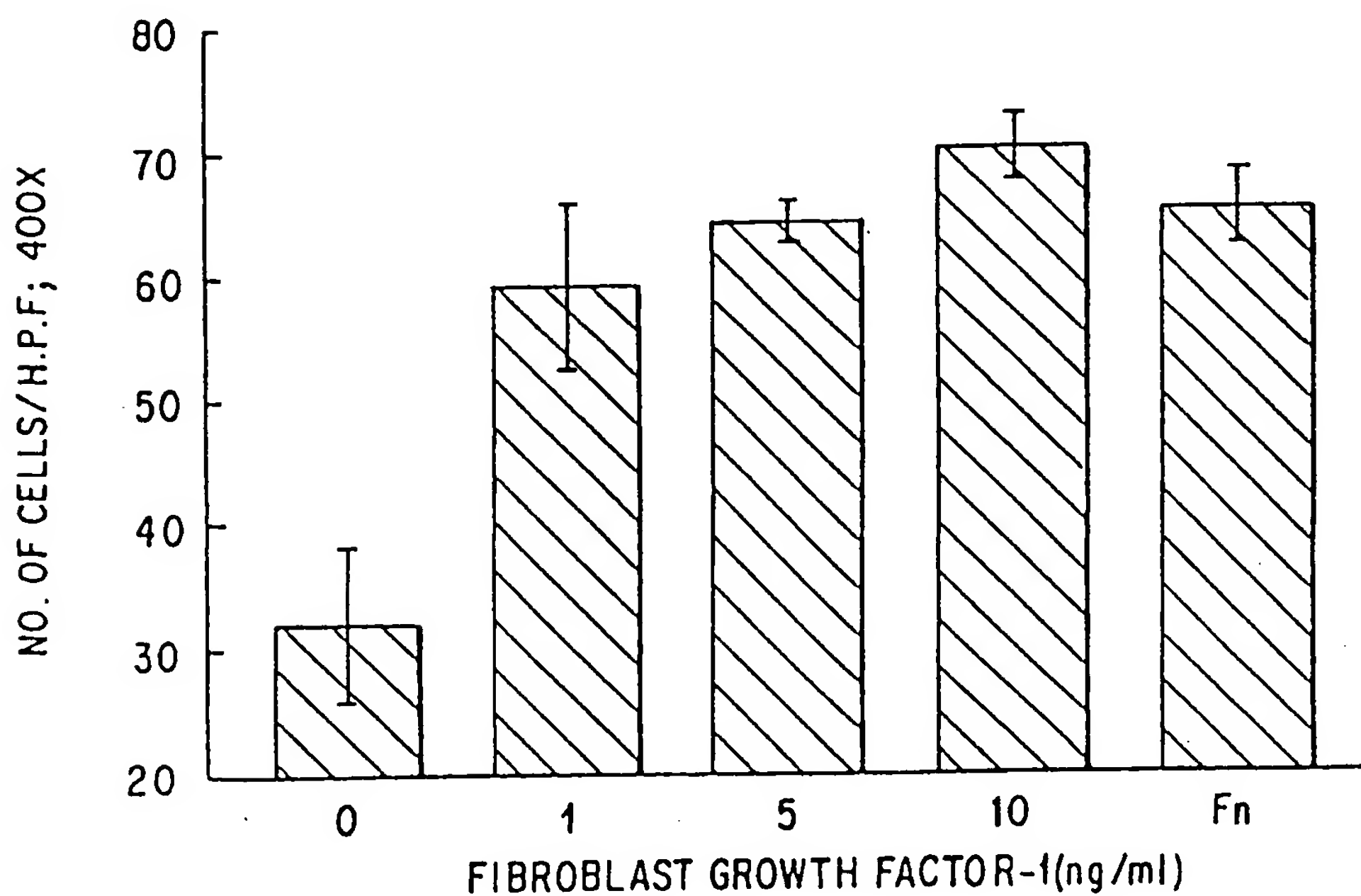


FIG. 32

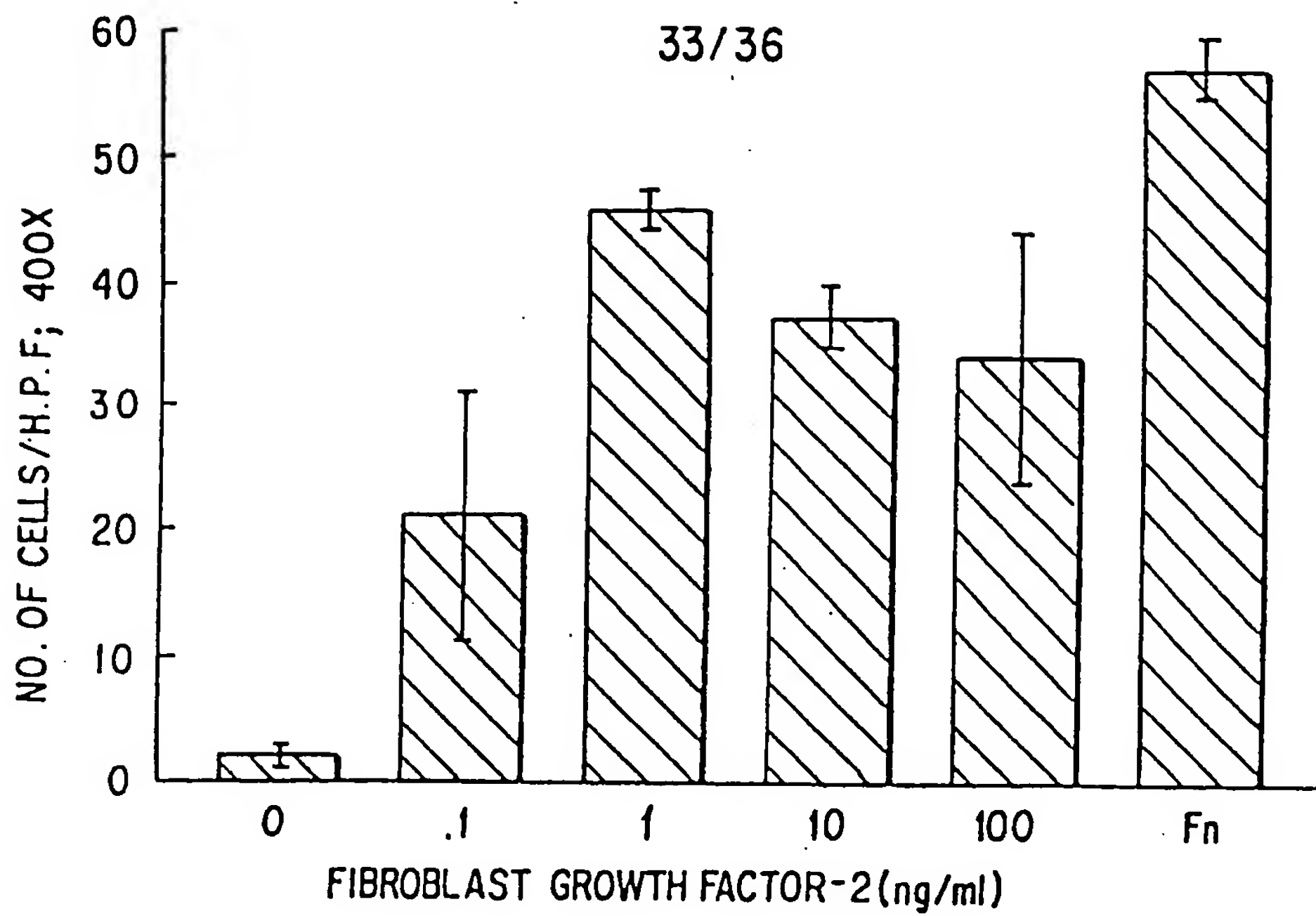
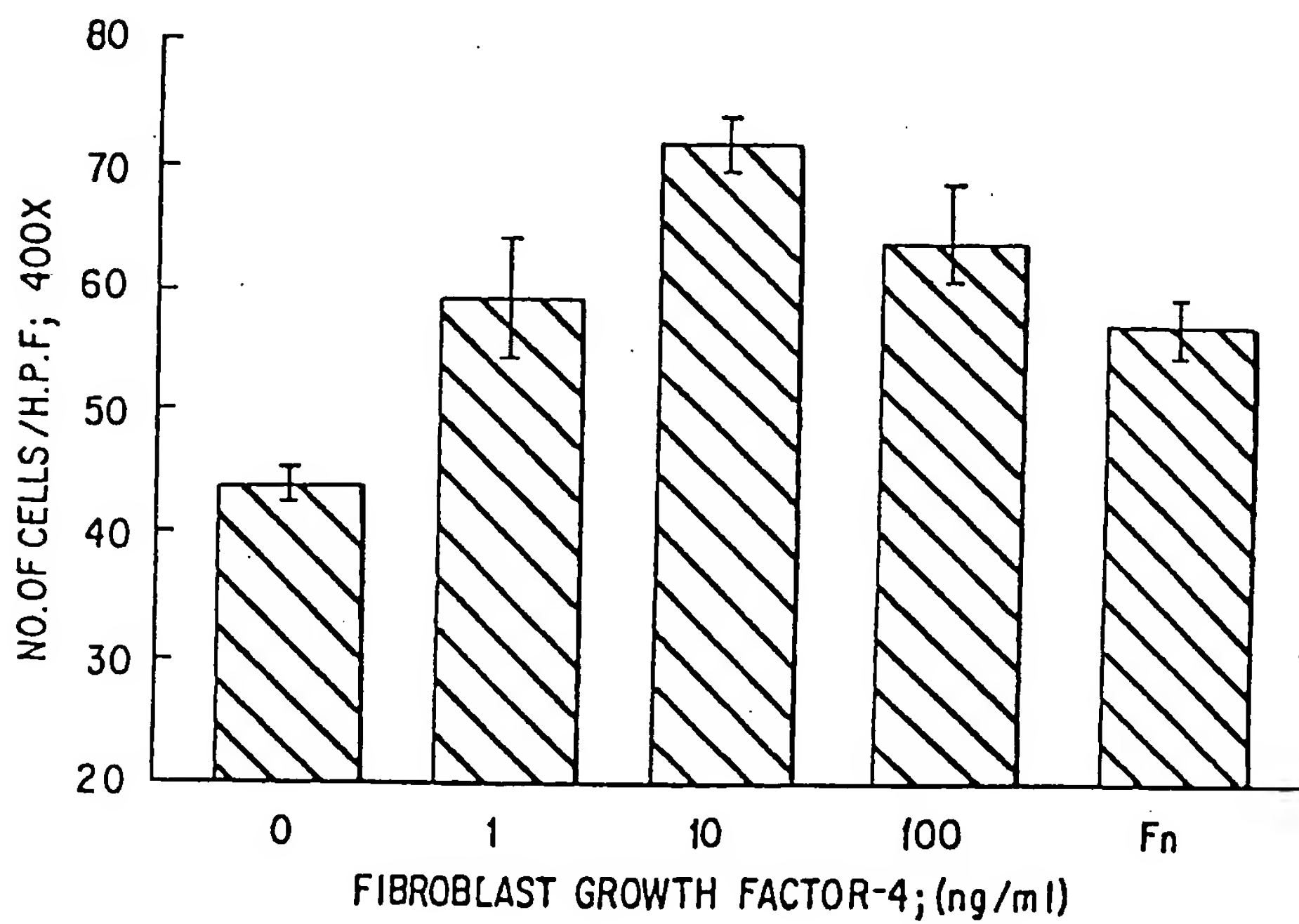


FS ALONE
FS+ETHANOL
BUFFER
FS+TAXOL SUSPENSION
FS+TAXOL SOLUTION (IN ETHANOL)

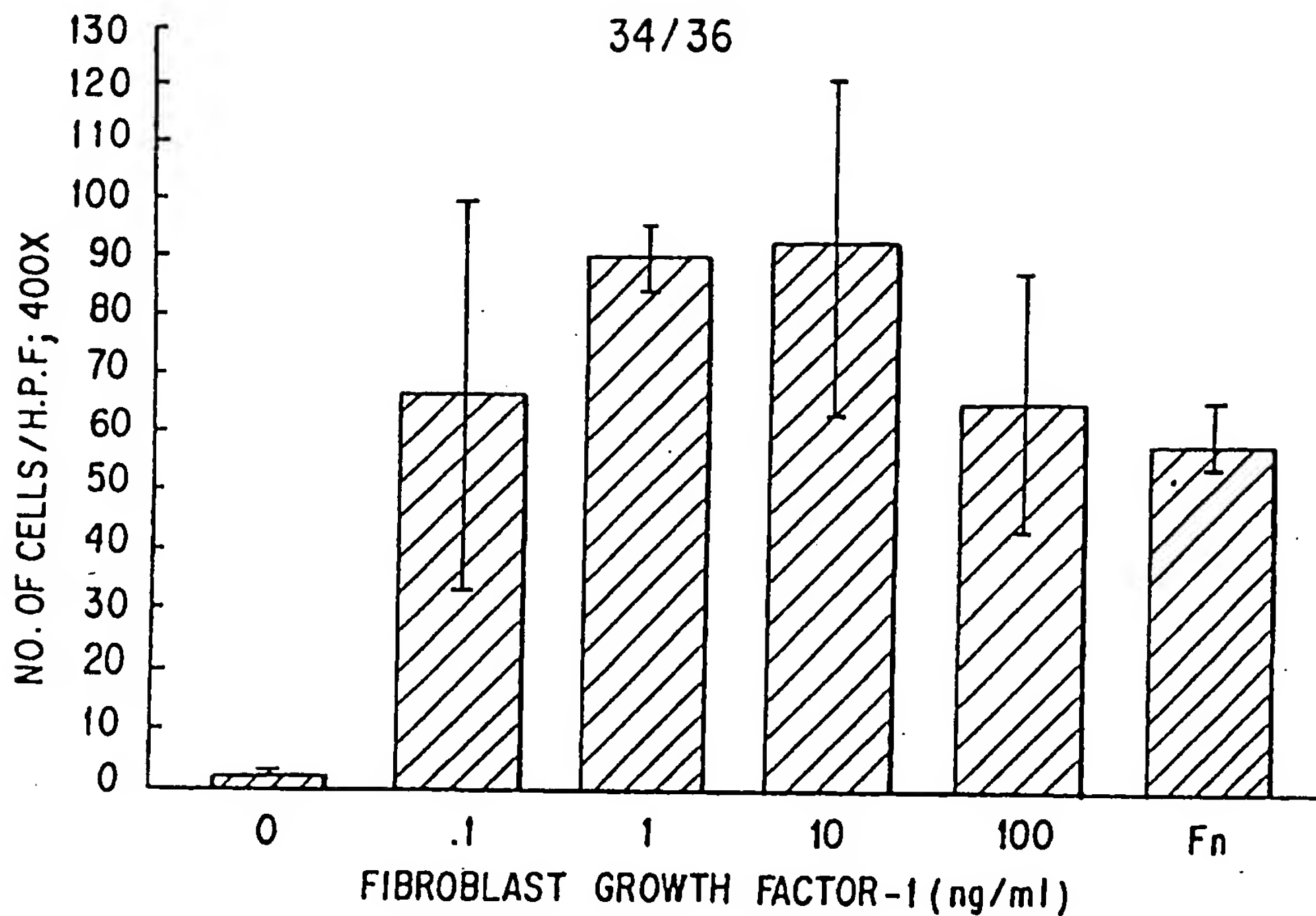
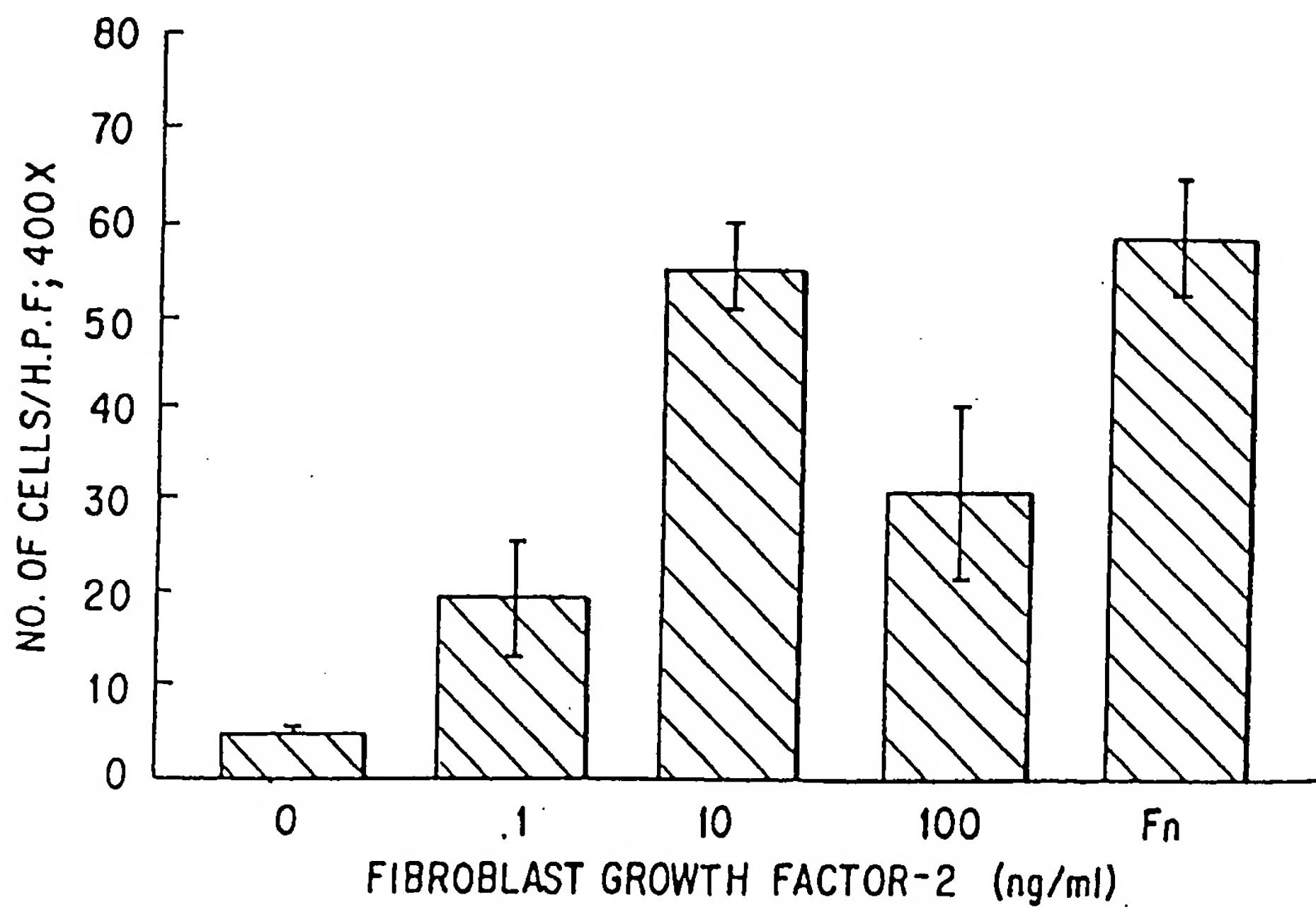
FIG. 33

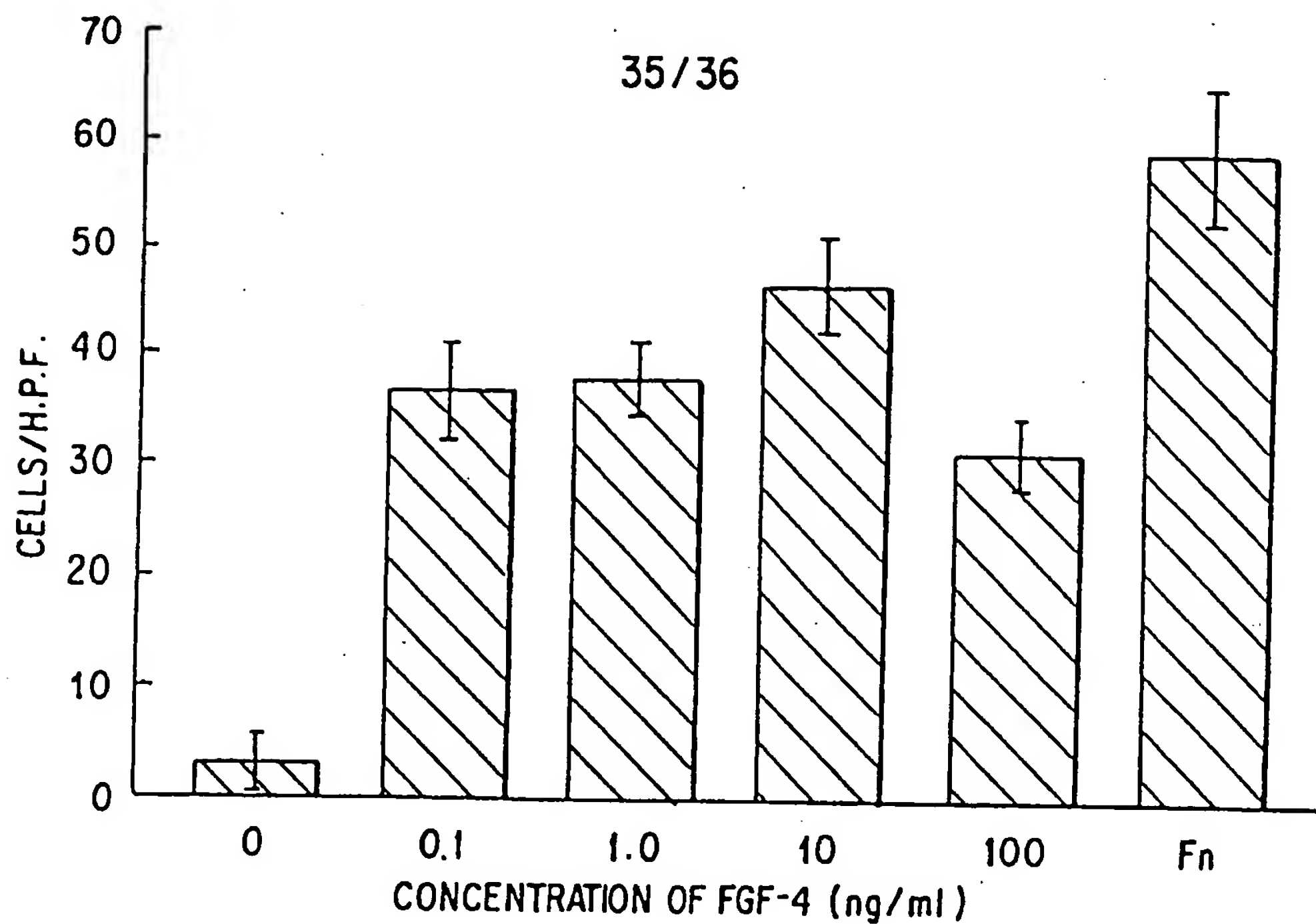
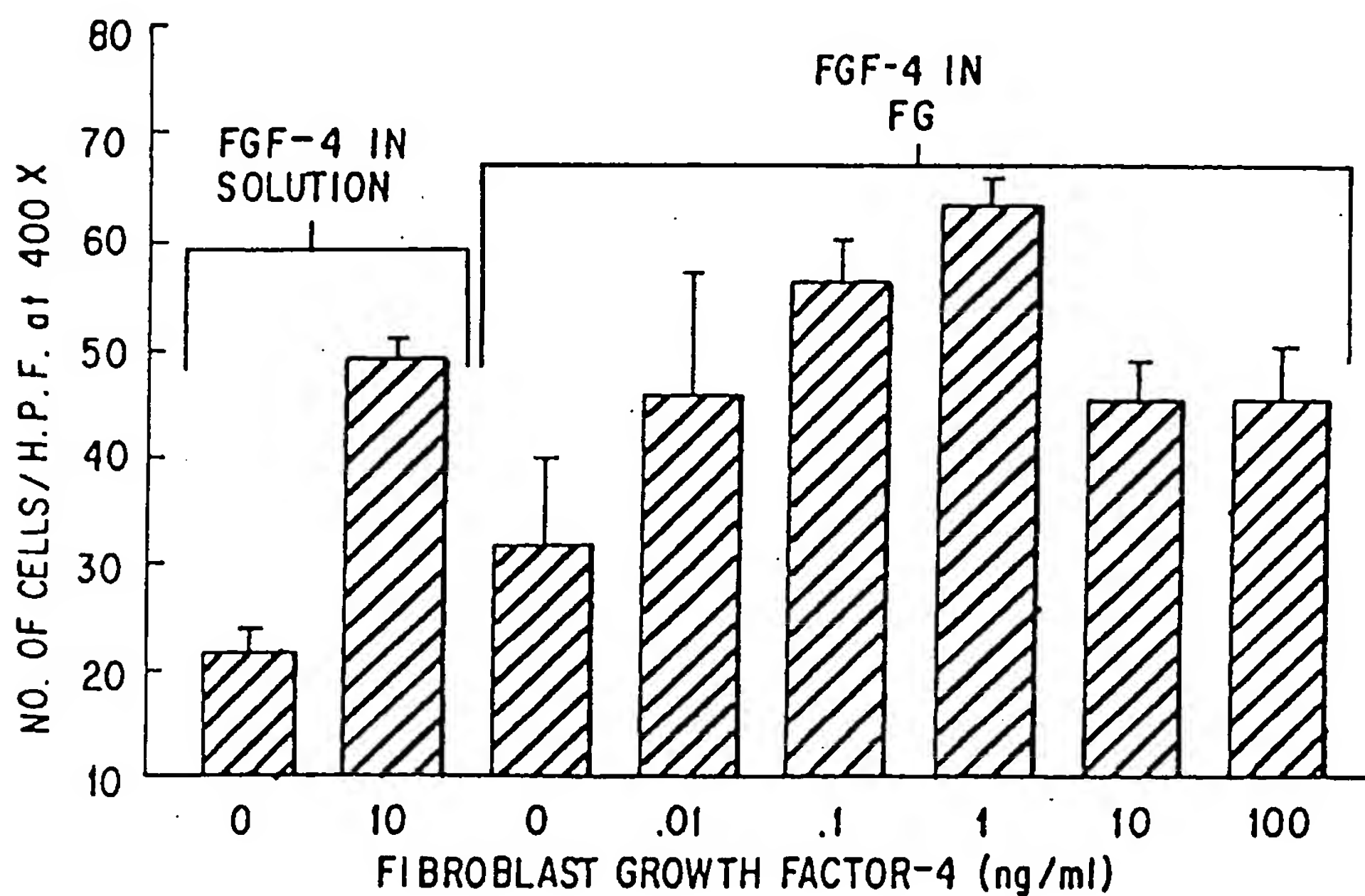
**FIG. 34****FIG. 35**

SUBSTITUTE SHEET (RULE 26)

**FIG. 36****FIG. 37**

SUBSTITUTE SHEET (RULE 26)

**FIG.38****FIG.39**

**FIG. 40****FIG. 41**

36/36

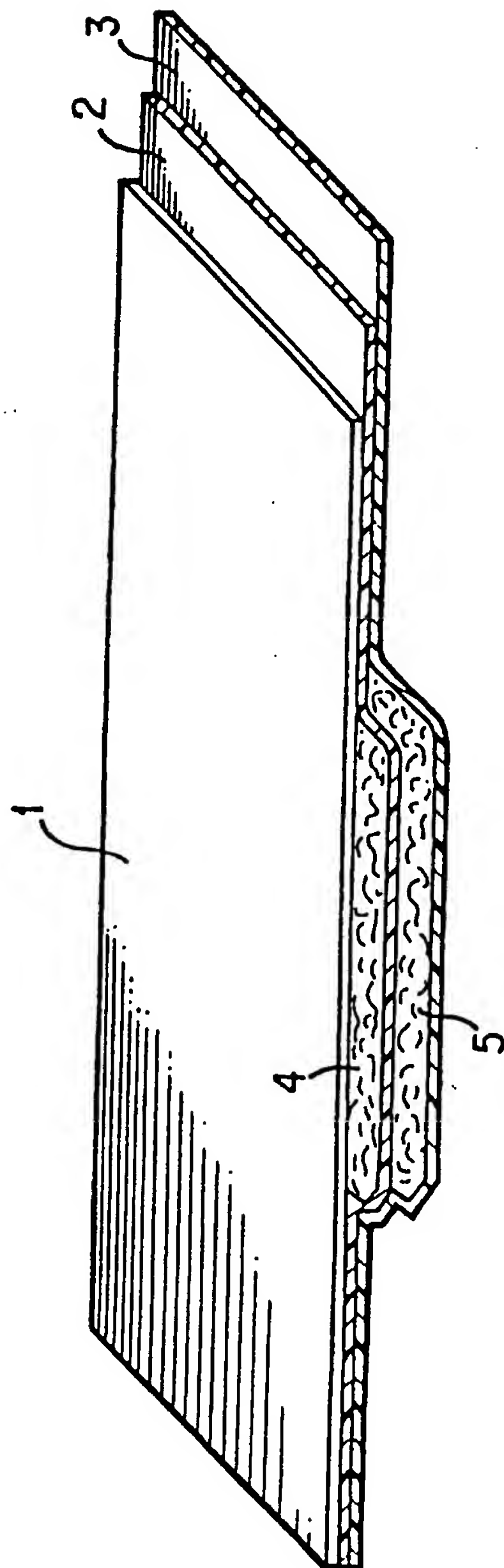


FIG. 42

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/10006

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 35/14, 38/43, 38/48; C12N 9/74; A61F 13/00, 15/00

US CL :424/94.1, 94.64; 602/48; 530/382; 435/214

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/94.1, 94.64; 602/48; 530/382; 435/214

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Medline, Embase, Biosis, CA, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,377,572 A (SCHWARZ ET AL.) 22 March 1983 (22.03.83), see entire patent.	1-7, 11, 39, 41-47, 51
Y	US 5,226,877 A (EPSTEIN) 13 July 1993 (13.07.93), see entire patent.	1-7, 18-36, 39, 41-47, 51
X --- Y	US 5,124,155 A (REICH) 23 June 1992 (23.06.92), see entire patent.	1-3, 5, 6, 8, 9, 17-30, 33, 34, 38-42, 44-47, 49, 51 ----- 4, 7, 10-16, 31, 32, 35-37, 43, 48, 50

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z*	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

26 AUGUST 1996

Date of mailing of the international search report

17 SEP 1996

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

Kristin K. Larson

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/10006

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>GERSDORFF, M.C.H. et al. A New Procedure for Bone Reconstruction in Oto-Microsurgery: A Mixture of Bone Dust and Fibrinogen Adhesive. Laryngoscope. October 1985, Vol. 95, No. 10, pages 1278-1280, see entire article.</p>	37, 45
Y	<p>HARTING, F. et al. Glued Fixation of Split-Skin Graft to the Bony Orbit Following Exenteration. Plastic and Reconstructive Surgery. October 1985, Vol. 76, No. 4, pages 633-635, see entire article.</p>	1-7, 41, 42, 46, 51
Y	<p>WO 93/05067 A1 (BAXTER INTERNATIONAL, INC.) 18 March 1993, pages 10 -12.</p>	18-24, 29-35, 51
Y	<p>WEISMAN, R.A. et al. Biochemical Characterization of Autologous Fibrinogen Adhesive. Laryngoscope. October 1987, Vol. 97, No. 10, pages 1186-1190, see entire article.</p>	1-7, 11, 13, 39, 41, 42, 44, 46-48, 51
A	<p>THOMPSON, D.F. et al. Fibrin Glue: A Review of its Preparation, Efficacy, and Adverse Effects as a Topical Hemostat. Drug Intelligence and Clinical Pharmacy. December 1988, Vol. 22, No. 12, pages 946-952.</p>	1-51
A	<p>EPSTEIN, G.H. et al. A New Autologous Fibrinogen-Based Adhesive for Otologic Surgery. Ann. Otol. Rhinol. Laryngol. January/February 1986, Vol. 95, No. 1, Part 1, pages 40-45.</p>	1-51
A	<p>IKOSSI-O'CONNOR, M.G. et al. The Role of Fibrin Adhesive in Vascular Surgery. Journal of Surgical Oncology. July 1983, Vol. 23, No. 3, pages 151-152.</p>	1-51
A	<p>THORSON, G.K. et al. The Role of the Tissue Adhesive Fibrin Seal (FS) in Esophageal Anastomoses. Journal of Surgical Oncology. November 1983, Vol. 24, No. 3, pages 221-223.</p>	1-51
A	<p>PETRELLI, N.J. et al. The Application of Tissue Adhesives in Small Bowel Anastomoses. Journal of Surgical Oncology. January 1982, Vol. 19, No. 1, pages 59-61.</p>	1-51

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/10006

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-51
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☒

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/10006

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-50, drawn to a fibrin sealant bandage, to methods of treating wounded tissue in a patient, and to a method of preparing a fibrin sealant bandage.

Group II, claim 51, drawn to a supplemented fibrin sealant matrix.

Group III, claims 52-77, drawn to a fibrin sealant dressing.

Group IV, claim 78, drawn to a method of preparing a fibrin sealant dressing.

Group V, claims 79-84, drawn to a method of preparing a fibrin sealant dressing.

Group VI, claim 85, drawn to a method of preparing a fibrin sealant dressing.

Group VII, claim 86, drawn to a method of preparing a fibrin sealant dressing.

Group VIII, claim 87, drawn to a method of preparing a fibrin sealant dressing.

Group IX, claim 88, drawn to a method of preparing a fibrin sealant dressing.

Group X, claims 89 and 90, drawn to a method of treating wounded tissue in a patient.

Group XI claims 91 and 92, drawn to a fibrin sealant dressing.

Group XII claim 93, drawn to a method of treating wounded tissue in a patient.

Group XIII claim 94, drawn to a method of treating wounded tissue.

Group XIV, claim 95, drawn to a method of preparing a fibrin sealant dressing.

Group XV, claim 96, drawn to a fibrin matrix.

The inventions listed as Groups I-XV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups I, IV-IX, and XIV are directed to methods of preparing a fibrin sealant dressing. The methods require different ingredients and steps demonstrating that more than one method exists to prepare a fibrin sealant dressing. One would not have to practice any of the methods together to successfully practice just one method alone. Further, a different fibrin sealant would result from each method of preparation.

Groups I, X, XII, and XIII are directed to methods of treating wounded tissue. The methods require different ingredients and thus, demonstrate that more than one method can be used to treat wounded tissue using a fibrin sealant. One would not have to practice any of the methods together to successfully practice just one method alone. The methods of groups I, X, XII, and XIII do not share a special technical feature.

Groups I-III, XI, and XV are directed to various fibrin sealant compositions. These compositions contain different ingredients resulting in distinct compositions. The compositions of groups I-III, XI, and XV do not share a special technical feature.

All methods and sealants claimed are not linked by a special technical feature within the meaning of PCT Rule 13.2.

Accordingly, the groups do not relate to a single inventive concept under PCT Rule 13.1.

